Supporting Information

Synthesis, identification and structure-activity relationship analysis of GATA4 and NKX2-5 protein-protein interaction modulators

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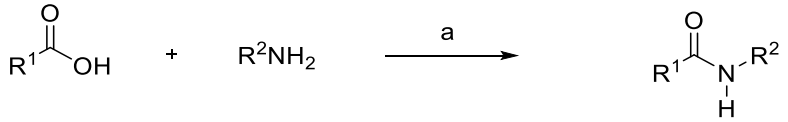
Table of Contents

Experimental Procedures (Chemistry)

All reactions were carried out using commercially available starting materials and reagents. Structures and synthesis of compounds **SI1-136** are shown in Supporting Information. Compound **1** was purchased from Pharmatory Ltd (Oulu, Finland). Compounds **SI120**–**130** and **59** were purchased from Enamine (Kiev, Ukraine), compounds **57**, **70** and **SI113** from ChemBridge (San Diego, California, USA), compounds **66**, **69** and **SI114-119** from ChemDiv (San Diego, California, USA) and compound **SI133-136** from Maybridge (Leicestershire, UK). All chemicals, solvents and anhydrous solvents used in the syntheses were acquired from Sigma-Aldrich (Schnelldorf, Germany), Fluka (Buchs, Switzerland) and Alfa Aesar (Ward Hill, Massachusetts, USA). All moisture sensitive reactions were performed in flame-dried glassware under an inert argon atmosphere. The progress of chemical reactions was monitored by thin-layer chromatography on 0.2-mm silica gel plates (silica gel 60, F254, Merck KGaA, Darmstadt, Germany) and visualized by UV light or ninhydrin stain (1.5% by weight in ethanol), when applicable. Column chromatography was performed with automated Biotage high performance flash chromatography Sp4-system (Uppsala, Sweden) using a 0.1-mm path length flow cell UV-detector/recorder module (fixed wavelength 254 nm) and the indicated mobile phase. The melting points were recorded with an SMP40 automatic melting point apparatus (Bibby Scientific Limited, Staffordshire, UK) and are uncorrected. Nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on a Varian Mercury Plus 300 (Agilent Technologies, Santa Clara, California, United States) or a Bruker Ascend 400 – Avance III HD NMR spectrometer (Bruker Corporation, Billerica, MA, USA), ^{1}H NMR spectra at 300 or 400 MHz and ^{13}C NMR spectra at 75 or 101 MHz. Chemical shifts (δ) are reported in parts per million (ppm) relative to the NMR solvent signals ($CDCl_3$ 7.26 and 77.16 ppm, DMSO-d_6 2.50 and 39.50 ppm, for ^{1}H and ^{13}C NMR, respectively. When necessary, two--dimensional NMR experiments (COSY, NOESY, gHSQC, gHMBC) were conducted to support structure determination. Multiplicities are indicated by s (singlet), d (doublet), dd (doublet of dublets), t (triplet), q (quartet), sept (septet). The additional letter "b" indicates a broad signal, such as bs (broad singlet). Multiplets (m) are either reported as a range of ppm values (m) or as a centered multiplet (m_c). Coupling constants *J* are quoted in Hertz (Hz). Exact mass and purity (>95%) of all tested compounds was confirmed by LC-MS analyses with a Waters Acquity® UPLC system (Waters, Milford, MA, USA) equipped with an Acquity UPLC® BEH C18 column (1.7 μm, 50 mm × 2.1 mm, Waters, Ireland), an Acquity PDA detector and a Waters Synapt G2 HDMS mass spectrometer (Waters, Milford, MA, USA) via an ESI ion source in positive mode. High resolution mass (HRMS-ESI) data was reported for the molecular ions $[M+H]^+$.

General procedure I: HBTU-mediated amide coupling

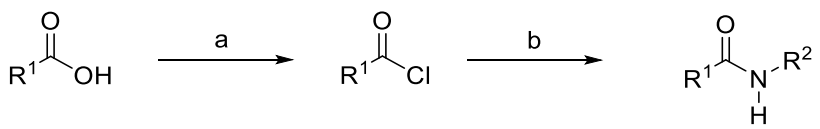
Unless otherwise noted, equimolar amounts of carboxylic acid, aromatic amine and the indicated amount of *N*,*N*,*N*′,*N*′-tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate (HBTU), typically between 1 and 3 equivalents, were dissolved under argon in anhydrous *N*,*N*-dimethylformamide (DMF). The given amount of *N*,*N*-diisopropylethylamine (DIPEA), typically between 1 and 3 equivalents, was added to the stirred reaction mixture at room temperature. Unless otherwise indicated, the work-up was started after the reaction mixture was stirred overnight. Either diethyl ether or ethyl acetate was added, and the organic phase was washed three times with water. When phase separation was slow, 5-30% of brine was added to the aqueous phase to aid separation. After drying the organic phase with anhydrous Na_2SO_4, the solvents were removed with a rotary evaporator. The crude product was either directly recrystallized from the solvent mixtures indicated or subjected to automated preparative chromatography. Unless otherwise indicated, the chromatography on silica gel was performed with an increasing gradient of ethyl acetate in *n*-hexane, starting with 0% of ethyl acetate.



Scheme 1. Synthesis of amides with various northern (R^2) and southern (R^1) parts. Reagents and conditions. a) HBTU DIPEA, DMF, rt, 1-2 d.

General procedure II: Acyl chloride-mediated amide synthesis

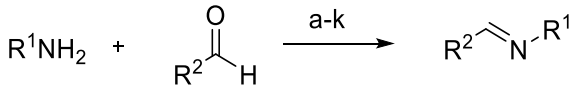
When the required acyl chloride was not commercially available, it was prepared according to the following procedure. Unless otherwise noted, one equivalent of carboxylic acid was dissolved in anhydrous dichloromethane under argon. Three equivalents of a 2 M solution of oxalyl choride in dichloromethane and a catalytic amount of anhydrous DMF (0.1 equiv) were added, and the reaction mixture was stirred for 2 h at room temperature. The solvent was removed with a rotary evaporator, and the residue was dissolved in anhydrous pyridine. The required amine was added, and the reaction mixture was stirred overnight at room temperature. Diethyl ether was added and the organic phase was washed three times with water. When phase separation was slow, 5-30% of brine was added to the aqueous phase to aid separation. The organic solvents were removed with a rotary evaporator. The crude product was either directly recrystallized from the solvent mixtures indicated or purified by automated preparative chromatography. Unless otherwise indicated, the chromatography on silica gel was performed with an increasing gradient of ethyl acetate in *n*-hexane, starting with 0% of ethyl acetate.



Scheme 2. Synthesis of acyl chlorides and amides. Reagents and conditions. a) $(COCl)_2$, DMF, DCM, rt, 2 h. b) R^2NH_2, py, rt, overnight.

General procedure III: Synthesis of Schiff bases

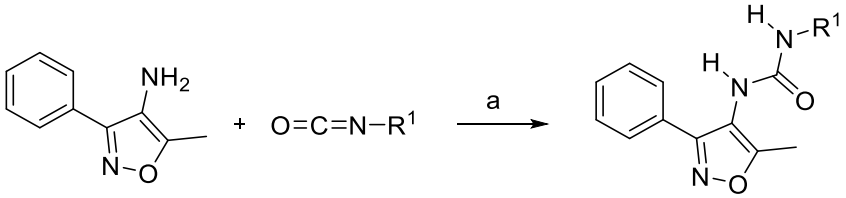
Unless otherwise noted, equimolar amounts of aldehyde and amine were dissolved in anhydrous toluene under argon. The indicated amount of anhydrous Na_2SO_4, typically 2 equivalents, and the indicated amount of acetic acid, typically 0.25 equivalents, were added. Generally, the resulting mixture was stirred at room temperature overnight or, if indicated, heated under reflux conditions for an appropriate time. When no sufficient conversion was observed by TLC, a small amount of *p*-toluenesulfonic acid was added as indicated, and the reaction mixture was stirred at room temperature or heated for the given time. The reaction mixture was then concentrated with a rotary evaporator and purified by automated preparative chromatography. Unless otherwise indicated, the chromatography on silica gel was performed with an increasing gradient of ethyl acetate in *n*-hexane, starting with 0% of ethyl acetate.



Scheme 3. Synthesis of Schiff bases with different northern (R^1NH_2) and southern (R^2CHO) parts. Reagents and conditions: AcOH, Na_2SO_4 anhydr., toluene. a) rt, overnight. b) reflux, 9 h. c) 1. 70 °C, 100 °C, 5 h. 2. *p*-TsOH, 70 °C, 30 min. d) additional ethyl acetate, 70 °C, overnight. e) rt, overnight, 70 °C, 2 h. f) additional *p*-TsOH 70 °C, 2 h. g) additional *p*-TsOH, 70 °C, 4 h. h) 100 °C, 6 h. i) *p*-TsOH, 90 °C, 4 h, 70 °C, overnight. j) 70 °C, overnight.

General procedure IV: Synthesis of ureas

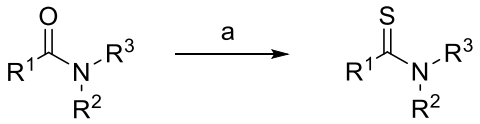
Unless otherwise noted, equimolar amounts of amine and isocyanate were dissolved in anhydrous toluene under argon, and the reaction mixture was stirred at room temperature overnight. The crude product was either directly recrystallized from the reaction mixture after addition of an appropriate amount of solvent. Alternatively, the solvent was removed with a rotary evaporator and the crude product was purified by automated preparative chromatography. Unless otherwise indicated, the chromatography on silica gel was performed with an increasing gradient of ethyl acetate in *n*-hexane, starting with 0% of ethyl acetate.



Scheme 4. Synthesis of ureas. Reagents and conditions. a) Toluene, rt, overnight to 4 d.

General procedure V: Synthesis of carbothioamides from amides

Unless otherwise noted, one equivalent of the approproate amide was dissolved in anhydrous toluene. Lawesson's reagent, 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide (0.6 equiv) was added and the resulting mixture was heated at reflux temperature for the time indicated or overnight. The reaction mixture was diluted with ethyl acetate and washed three times with water. The organic solvent was removed with a rotary evaporator and the crude product was purified by automated preparative chromatography. Unless otherwise indicated, the chromatography on silica gel was performed with an increasing gradient of ethyl acetate in *n*-hexane, starting with 0% of ethyl acetate.

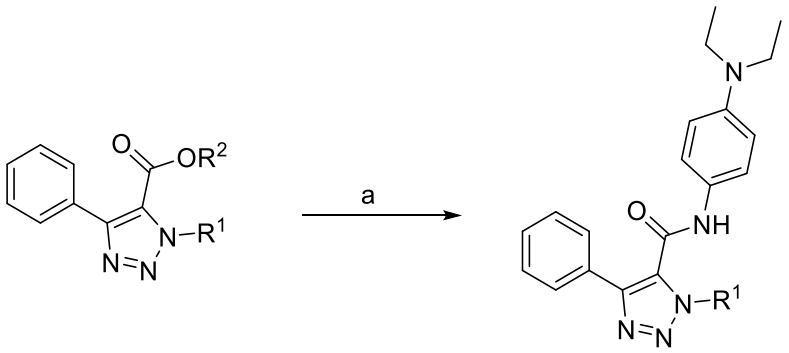


Scheme 5. Synthesis of carbothioamides. Reagents and conditions. a) Lawesson's reagent, toluene, reflux, 6 h to overnight.

General procedure VI: Hydrolysis of triazole esters and the subsequent HBTU-mediated amide coupling

Unless otherwise noted, one equivalent of triazole methyl ester was dissolved or suspended in an equimixture of THF, methanol and water. Lithum hydroxide monohydrate (1.5 equiv) was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate and the mixture was transferred to a separation funnel. Water was added and the mixture was acidified with 1 M hydrochloric acid. The phases were separated, the organic phase was washed neutral with portions of water and the solvent was removed with a rotary evaporator. After drying the crude intermediate, it was dissolved in anhydrous DMF under argon.

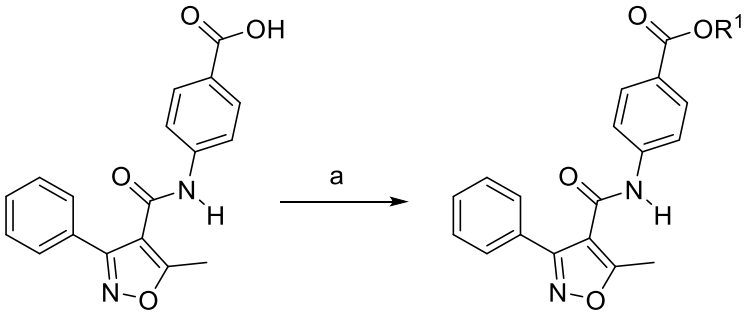
An equimolar amount of aromatic amine and the indicated amounts of HBTU (typically 1.3 equiv) and DIPEA (typically 2 equiv) were added to the above-mentioned solution of the crude carboxylic acid in DMF, and the reaction mixture was stirred at room temperature. Unless otherwise indicated, the work-up was started after the reaction mixture was stirred overnight. Either diethyl ether or ethyl acetate was added and the organic phase was washed three times with water. When phase separation was slow, 5-30% of brine was added to the aqueous phase. Organic solvents were removed with a rotary evaporator. The crude product was either directly recrystallized from the solvent mixtures indicated or subjected to automated preparative chromatography purification. Unless otherwise indicated, the chromatography on silica gel was performed with an increasing gradient of ethyl acetate in *n*-hexane, starting with 0% of ethyl acetate.



Scheme 6. Hydrolysis of triazole esters and the subsequent HBTU-mediated amide coupling. Reagents and conditions. a) 1. $LiOH{\cdot}H_2O$, THF/MeOH/H_2O (1:1:1), rt, overnight. 2. *N*,*N*-diethyl-1,4-phenylenediamine, HBTU, DIPEA, DMF, rt, 1-2 d.

General procedure VII: HBTU-mediated ester synthesis

Unless otherwise noted, aromatic carboxylic acid, alcohol (3 equiv) and HBTU (1.3–1.5 equiv) were dissolved in anhydrous DMF under argon. DIPEA (2 equiv) was added and the reaction mixture was stirred at room temperature. After the reaction time indicated, either diethyl ether or ethyl acetate was added and the organic phase was washed three times with water. When phase separation was slow, 5-30% of brine was added to the aqueous phase. The organic solvents were removed with a rotary evaporator. The crude product was purified by automated preparative chromatography. Unless otherwise indicated, the chromatography on silica gel was performed with an increasing gradient of ethyl acetate in *n*-hexane, starting with 0% of ethyl acetate.



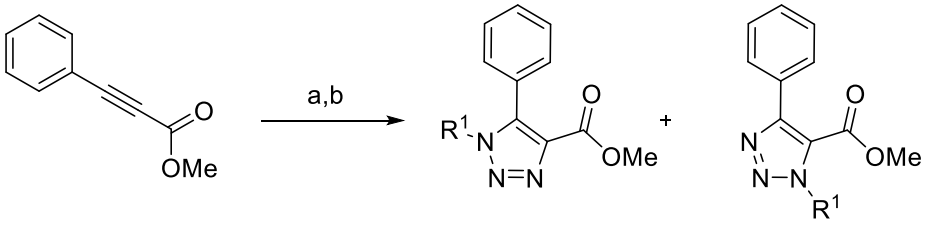
Scheme 7. HBTU-mediated ester synthesis. Reagents and conditions. a) R^1OH, HBTU, DIPEA, DMF, rt, 1-3 d.

General procedure VIII: Synthesis of 1,2,3-triazoles via 1,3-dipolar cycloaddition

Method A: Equimolar amounts of methyl phenylpropiolate, alkyl halide, tetra-*n*-butylammoniumbromide, TBAB and sodium azide were dissolved in a two-phase system of equal volumes of toluene and water. The reaction mixture was either pre-stirred at room temperature as indicated, or irradiated directly in a microwave reactor (typically at 150 °C for 60 min). The phases were separated, and the aqueous phase was washed with toluene or ethyl acetate as indicated. The organic solvent was removed with a rotary evaporator. The crude product was purified by automated

preparative chromatography. Unless otherwise indicated, the chromatography on silica gel was performed with an increasing gradient of ethyl acetate in *n*-hexane, starting with 0% of ethyl acetate.

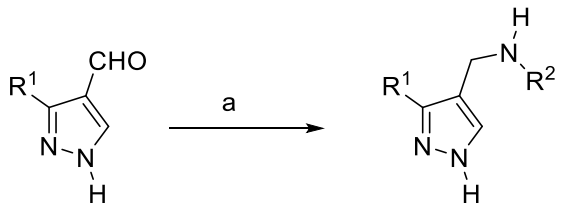
Method B: Equimolar amounts of methyl phenylpropiolate, alkyl halide and sodium azide were dissolved in absolute DMF. The reaction mixture was irradiated in a microwave reactor (typically at 140 °C for 70 min). The reaction mixture was diluted with ethyl acetate and washed three times with water. When phase separation was slow, 5-30% of brine was added to the aqueous phase. The organic solvents were removed with a rotary evaporator. The crude product was purified by automated preparative chromatography. Unless otherwise indicated, the chromatography on silica gel was performed with an increasing gradient of ethyl acetate in *n*-hexane, starting with 0% of ethyl acetate.



Scheme 8. Synthesis of 1,2,3-triazoles via 1,3-dipolar cycloaddition. Reagents and conditions. a) R^1Br or R^1I, NaN_3, toluene, H_2O, TBAB, rt or MW (150 °C, 60 min) or b) R^1Br or R^1I, NaN_3, DMF, MW (140 °C, 70 min).

General procedure IX: Reductive amination of aldehydes via Schiff bases

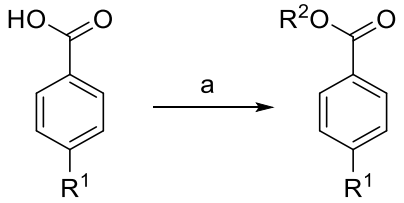
Unless otherwise noted, anhydrous sodium sulphate (3 equiv) was flame-dried in an evacuated Schlenk flask. Absolute THF, acetic acid (0.25–1 equiv) as well as an equimolar amount of aromatic aldehyde and aromatic amine were added to the flask containing Na_2SO_4. The reaction mixture was stirred at room temperature for the indicated time, and a 1.0 M solution of sodium cyanoborohydride in THF (3-5 equiv) was added. The solution was stirred at room temperature until TLC indicated consumption of the starting materials and intermediate Schiff base (3-5 d). During this period of time additional sodium cyanoborohydride may be added (1-2 equiv). The reaction mixture was quenched with a diluted solution of sodium hydroxide in water or a saturated solution of sodium hydrogencarbonate in water. After 20-60 min ethyl acetate was added, and the organic phase was washed three times with a mixture of water and brine (typically 2:1). The organic solvents were removed with a rotary evaporator. The crude product was purified by automated preparative chromatography. The chromatography on silica gel was performed with an increasing gradient of ethyl acetate containing triethylamine (1%) in *n*-hexane, starting with 0% of ethyl acetate-triethylamine mixture.



Scheme 9. Reductive amination of aldehydes via Schiff base. Reagents and conditions. a) 1. $NaBH_3CN$, Na_2SO_4, rt, 3 d, 2. additional $NaBH_3CN$, rt, overnight.

General procedure X: Ester synthesis by alkylation of aromatic carboxylic acids

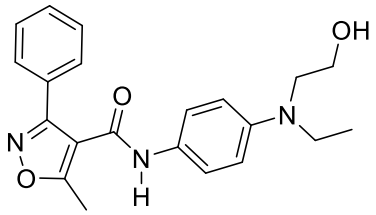
Unless otherwise noted, the appropriate carboxylic acid was dissolved in absolute DMF under argon. Alkyl halide (3 equiv) and potassium carbonate (2 equiv) were added, and the reaction mixture was shaken in a sealed tube at room temperature (1-4 d). Ethyl acetate was added and the organic phase was washed three times with a mixture of water and brine (3:1). The organic solvents were removed with a rotary evaporator, and the crude product was purified by automated preparative chromatography. The chromatography on silica gel was performed with an increasing gradient of ethyl acetate in *n*-hexane, starting with 0% of the ethyl acetate.



Scheme 10. Alkylation of aromatic carboxylic acids to produce the corresponding esters. a) R^2 Br or R^2 I, K_2CO_3, DMF, rt, 1-4 d.

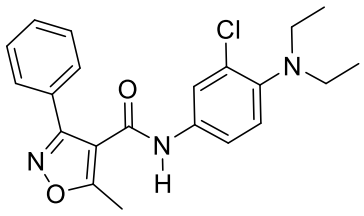
Preparation of compounds in Scheme 1 and other related compounds

***N*-[4-[Ethyl(2-hydroxyethyl)amino]phenyl]-5-methyl-3-phenylisoxazole-4-carboxamide (4b)**



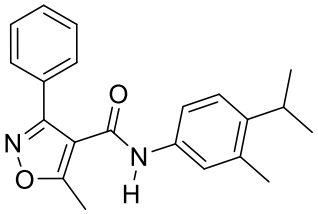
Synthesis according to the General procedure I. 5-Methyl-3-phenylisoxazole-4-carboxylic acid (345 mg, 1.70 mmol), 4-amino-*N*-(2-hydroxyethyl)-*N*-ethylaniline sulfate **2b** (473 mg, 1.70 mmol), HBTU (838 mg, 2.21 mmol, 1.3 equiv), DIPEA (1.18 mL, 6.80 mmol, 4 equiv), DMF (5 mL). Solvent for extraction: ethyl acetate. Recrystallization (MeOH/H_2O 10+1) after chromatography on silica gel gave compound **4b** (221 mg, 0.605 mmol, 36%) as beige crystals. M.p. 155.0–157.5 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.10 (s, 1H), 7.74–7.66 (m, 2H), 7.53–7.44 (m, 3H,), 7.38 (m$_c$, 2H), 6.63 (m$_c$, 2H), 4.68 (t, 1H, ^3J = 5.4 Hz), 3.51 (q, 2H, ^3J = 6.0 Hz), 3.39–3.26 (m, 4H), 2.55 (s, 3H) 1.05 (t, 3H, ^3J = 7.0 Hz) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 169.4, 160.1, 159.1, 144.8, 130.1, 128.9, 128.2, 127.7, 127.1, 121.5, 113.6, 111.4, 58.4, 52.3, 44.7, 11.9, 11.9 ppm. HRMS calc. for $C_{21}H_{24}N_3O_3$ $[M+H]^+$: 366.1818, found 366.1817.

***N*-[3-Chloro-4-(diethylamino)phenyl]-5-methyl-3-phenylisoxazole-4-carboxamide (4c)**



Synthesis according to the General procedure I. 5-Methyl-3-phenylisoxazole-4-carboxylic acid (0.100 g, 0.492 mmol), 2-chloro-N^1,N^1-diethyl-1,4-phenylenediamine (116 mg, 0.492 mmol), HBTU (243 mg, 0.640 mmol, 1.3 equiv), DIPEA (0.257 mL, 1.48 mmol, 3 equiv), DMF (3 mL). Solvent for extraction: ethyl acetate and a mixture of water and brine (3:1). Recrystallization (MeOH/H_2O 10+1) after chromatography on silica gel gave compound **4c** (96.7 mg, 0.252 mmol, 51%) as white needles. M.p. 153.9–155.4 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.44 (s, 1H), 7.80 (d, 1H, ^4J = 2.4 Hz), 7.73–7.65 (m, 2H), 7.54–7.41 (m, 4H), 7.18 (d, 1H, ^3J = 8.7 Hz), 3.01 (q, 4H, ^3J = 7.0 Hz), 2.58 (s, 3H), 0.94 (t, 3H, ^3J = 7.0 Hz) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 169.9, 160.1, 159.8, 143.2, 134.4, 130.0, 129.7, 128.8, 127.9, 127.7, 124.0, 121.2, 118.7, 113.1, 46.2, 12.0, 11.9 ppm. HRMS calc. for $C_{21}H_{23}ClN_3O_2$ $[M+H]^+$: 384.1479, found 384.1481.

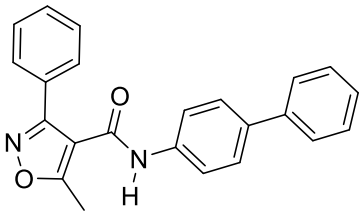
***N*-(4-Isopropyl-3-methylphenyl)-5-methyl-3-phenylisoxazole-4-carboxamide (4e)**



Synthesis according to the General procedure I. Deviating from the General procedure I, the reaction mixture was diluted with ethyl acetate for the work-up and extracted in the following order: once with water containing 10% brine, once with a 2 M solution of sodium hydroxide in water, once with 2 M hydrochloric acid and several times with water until the water phase remained neutral. 5-Methyl-3-phenylisoxazole-4-carboxylic acid, **6**, (82.1 mg, 0.404 mmol), 4-isopropyl-3-methylaniline hydrochloride (75.0 mg, 0.404 mmol), HBTU (383 mg, 1.01 mmol, 2.5 equiv), DIPEA (0.282 mL, 1.62 mmol, 4 equiv), DMF

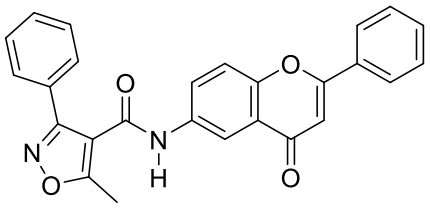
(3 mL). Recrystallization (MeOH/H_2O 10+1) after automated chromatography on silica gel gave compound **4e** (78.0 mg, 0.233 mmol, 58%) as fine white needles. M.p. 147.0–148.5 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.32 (s, 1H), 7.72–7.66 (m, 2H), 7.53–7.47 (m, 3H), 7.42–7.37 (m, 2H), 7.21–7.16 (m, 1H), 3.06 (sept, 1H, ^3J = 6.8 Hz), 2.56 (s, 3H), 2.27 (s, 3H), 1.15 (d, 6H, ^3J = 6.8 Hz) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 169.7, 160.1, 159.7, 142.3, 136.0, 134.9, 130.1, 128.9, 128.1, 127.7, 124.9, 121.3, 117.7, 113.4, 28.3, 23.2, 19.1, 11.9 ppm. HRMS calc. for $C_{21}H_{23}N_2O_2$ $[M+H]^+$: 335.1760, found 335.1759.

_N_-[[1,1'-Biphenyl]-4-yl]-5-methyl-3-phenylisoxazole-4-carboxamide (4f)



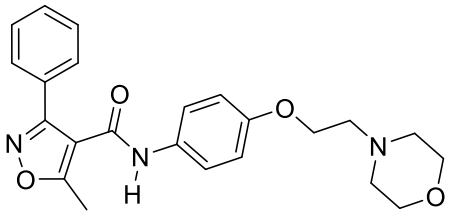
Synthesis according to the General procedure I. Deviating from the General procedure I, the reaction time was 2 d and the reaction mixture was diluted with ethyl acetate for the work-up and extracted in the following order: once with water, twice with a 2 M solution of sodium hydroxide in water, twice with 4 M hydrochloric acid and several times with water until the aqueous phase remained neutral. 5-Methyl-3-phenylisoxazole-4-carboxylic acid **6** (203 mg, 1.00 mmol), 4-aminobiphenyl (169 mg, 1.00 mmol), HBTU (455 mg, 1.20 mmol, 1.2 equiv), DIPEA (0.348 mL, 2.00 mmol, 2 equiv), DMF (2 mL). Recrystallization, MeOH (10 mL)/2-propanol (5 mL)/ethyl acetate (5 mL), [without chromatography on silica gel] gave compound **4f** (283 mg, 0.799 mmol, 80%) as fine white needles. M.p. 192.7–194.3 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.54 (s, 1H), 7.76–7.62 (m, 8H), 7.53–7.42 (m, 5H), 7.37–7.31 (m, 1H), 2.60 (s, 3H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 169.8, 160.1, 159.9, 139.6, 138.0, 135.8, 130.4, 128.8, 128.8, 128.0, 127.7, 127.1, 127.0, 126.3, 120.0, 113.3, 11.9 ppm. HRMS calc. for $C_{23}H_{19}N_2O_2$ $[M+H]^+$: 355.1447, found 355.1453.

5-Methyl-_N_-(4-oxo-2-phenyl-4_H_-chromen-6-yl)-3-phenylisoxazole-4-carboxamide (4g)



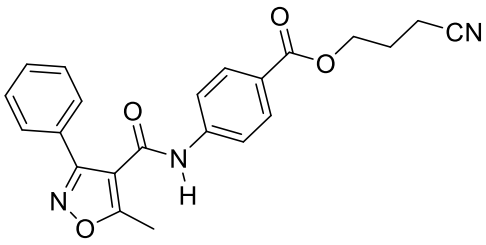
Synthesis according to the General procedure I. Deviating from the General procedure I, the crude product was first recrystallized from EtOAc/EtOH (2+1), and the mother liquor was purified by automated chromatography. The product obtained from chromatography on silica gel and the first recrystallization were combined and recrystallized again (EtOAc/EtOH 2+1). 5-Methyl-3-phenylisoxazole-4-carboxylic acid **6** (203 mg, 1.00 mmol), 6-aminoflavone (237 mg, 1.00 mmol), HBTU (493 mg, 1.30 mmol, 1.3 equiv), DIPEA (0.348 mL, 2.00 mmol, 2 equiv), DMF (2.5 mL). Solvent for extraction: ethyl acetate. Recrystallization (EtOAc/EtOH 2+1) after chromatography on silica gel gave compound **4g** (278 mg, 0.658 mmol, 66%) as slightly yellow crystals. M.p. 228.0–229.4 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.71 (s, 1H), 8.41 (d, 1H, ^3J = 2.7 Hz), 8.15–8.07 (m, 2H), 7.99 (dd, 1H, ^3J = 9.1 Hz), 7.80 (d, 1H), 7.76–7.68 (m, 2H), 7.66–7.55, 7.54–7.46 (each m, each 3H), 7.03 (s, 1H), 2.63 (s, 3H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 176.8, 170.2, 162.4, 160.2, 160.1, 152.1, 135.9, 131.7, 131.1, 130.1, 129.1, 128.8, 127.9, 127.7, 126.3, 126.2, 123.5, 119.6, 114.2, 113.0, 106.5, 11.9 ppm. HRMS calc. for $C_{26}H_{19}N_2O_4$ $[M+H]^+$: 423.1345, found 423.1347.

5-Methyl-*N*-[4-(2-morpholinoethoxy)phenyl]-3-phenylisoxazole-4-carboxamide (4h)



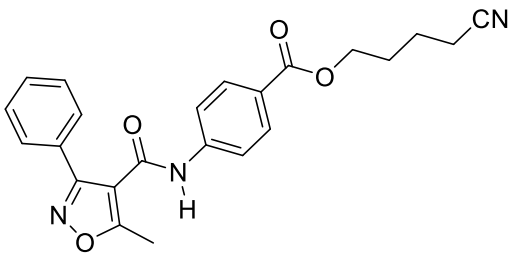
Synthesis according to the General procedure I. Deviating from the general procedure I, the reaction time was 3 h and reaction temperature was 60 °C. Deviating from the General procedure I, the reaction mixture was diluted with ethyl acetate for the work-up, and extracted twice with 2 M hydrochloric acid. The combined aqueous phases were made alkaline with a 2 M solution of sodium hydroxide in water and extracted twice with ethyl acetate. The combined organic phases were washed twice with a mixture of water and brine (10:1). 5-Methyl-3-phenylisoxazole-4-carboxylic acid (0.100 g, 0.492 mmol), 4-(2-morpholin-4-ylethoxy)aniline (109 mg, 0.492 mmol), HBTU (373 mg, 0.984 mmol, 2 equiv), DIPEA (0.257 mL, 1.48 mmol, 3 equiv), DMF (5 mL). Recrystallization (MeOH/H_2O 10+1) [without chromatography on silica gel] gave compound **4h** (102 mg, 0.250 mmol, 51%) as crystalline needles. M.p. 135.9–136.3 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.26 (s, 1H), 7.73–7.67 (m, 2H), 7.55–7.45 (m, 5H), 6.92 (m, 2H), 4.06 (t, 2H, J = 5.8 Hz), 3.58 (m, 4H), 2.67 (t, 2H, J = 5.8 Hz), 2.57 (s, 3H), 2.46 (m, 4H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 169.7, 160.1, 159.5, 155.0, 131.7, 130.1, 128.9, 128.1, 127.7, 121.1, 114.6, 113.4, 66.2, 65.5, 57.0, 53.6, 11.9 ppm. HRMS calc. for $C_{23}H_{26}N_3O_4$ $[M+H]^+$: 408.1923, found 408.1920.

3-Cyanopropyl 4-(5-methyl-3-phenylisoxazole-4-carboxamido)benzoate (10b)



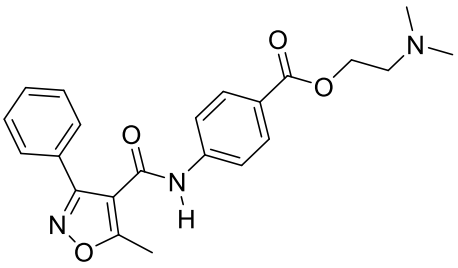
Synthesis according to the General procedure X. Deviating from the General procedure X, the chromatography was omitted and the product was recrystallized from MeOH/H_2O (10+1). 4-(5-Methyl-3-phenylisoxazole-4-carboxamido)benzoic acid **12** (40.1 mg, 0.124 mmol), bromobutanenitrile (12.4 μL, 0.124 mmol), K_2CO_3 (25.7 mg, 0.186 mmol, 1.5 equiv), DMF (1 mL). Reaction time: 2 d. Solvent for extraction: ethyl acetate and water. Recrystallization gave compound **10b** (41.0 mg, 0.105 mmol, 85%) as colorless needles. M.p. 170.6–172.5 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.73 (s, 1H), 8.00 (m_c, 2H), 7.75 (m_c, 2H), 7.71–7.64 (m, 2H), 7.53–7.45 (m, 3H), 4.32 (t, 2H, ^3J = 6.1 Hz), 2.68 (t, 2H, ^3J = 7.1 Hz), 2.60 (s, 3H), 2.03 (m_c, 2H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 170.3, 165.1, 160.3, 160.2, 142.9, 130.4, 130.1, 128.8, 127.9, 127.7, 124.6, 120.2, 119.0, 113.0, 63.0, 24.2, 13.5, 11.9 ppm. HRMS calc. for $C_{22}H_{20}N_3O_4$ $[M+H]^+$: 390.1454, found 390.1458.

4-Cyanobutyl 4-(5-methyl-3-phenylisoxazole-4-carboxamido)benzoate (10c)



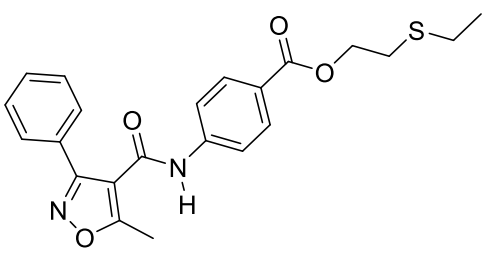
Synthesis according to the General procedure X. Deviating from the General procedure X, the chromatography was omitted and the product was recrystallized from MeOH. 4-(5-Methyl-3-phenylisoxazole-4-carboxamido)benzoic acid **12** (44.0 mg, 0.137 mmol), bromopentanenitrile (15.8 µL, 0.137 mmol), K_2CO_3 (28.4 mg, 0.206 mmol, 1.5 equiv), DMF (1 mL), Reaction time: 2 d. Solvent for extraction: ethyl acetate and water. Recrystallization gave compound **10c** (43.2 mg, 0.107 mmol, 78%) as a white solid. M.p. 114.0–115.4 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.73 (s, 1H), 7.96 (m$_c$, 2H), 7.76 (m$_c$, 2H), 7.72–7.64 (m, 2H), 7.53–7.45 (m, 3H), 4.29 (t, 2H, ^3J = 6.1 Hz), 2.60 (s, 3H), 2.58 (t, 2H, ^3J = 6.8 Hz), 1.87–1.64 (m, 4H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 170.3, 165.1, 160.3, 160.2, 142.9, 130.2, 130.1, 128.8, 127.9, 127.7, 124.9, 120.5, 119.1, 113.0, 63.6, 27.3, 21.7, 15.9, 11.9 ppm. HRMS calc. for $C_{23}H_{22}N_3O_4$ $[M+H]^+$: 404.1610, found 404.1613.

2-(Dimethylamino)ethyl 4-(5-methyl-3-phenylisoxazole-4-carboxamido)benzoate (10d)



Synthesis according to the General procedure VII. Deviating from the General procedure VII, the chromatography was performed with an increasing gradient of ethyl acetate containing TEA (1%) in *n*-hexane. 4-(5-Methyl-3-phenylisoxazole-4-carboxamido)benzoic acid **12** (31.4 mg, 0.0974 mmol), 2-(dimethylamino)ethan-1-ol (29.4 µL, 0.292 mmol, 3 equiv), HBTU (48.0 mg, 0.127 mmol, 1.3 equiv), DIPEA (33.9 µL, 0.195 mmol, 2 equiv), DMF (1 mL). Reaction time: 3 d. Solvent for extraction: ethyl acetate and a mixture of water and brine (2:1). Chromatography on silica gel gave compound **10d** (32.1 mg, 0.0816 mmol, 84%) as a yellowish solid. M.p. 95.8–99.5 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.73 (s, 1H), 7.95 (m$_c$, 2H), 7.76 (m$_c$, 2H), 7.72–7.64 (m, 2H), 7.53–7.45 (m, 3H), 4.34 (t, 2H, ^3J = 5.7 Hz), 2.64–2.58 (m, 5H), 2.21 (s, 6H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 170.3, 165.1, 160.3, 160.2, 142.8, 130.2, 130.1, 128.8, 127.9, 127.7, 124.9, 119.1, 113.0, 62.4, 57.2, 45.3, 11.9 ppm. HRMS calc. for $C_{22}H_{24}N_3O_4$ $[M+H]^+$: 394.1767, found 394.1772.

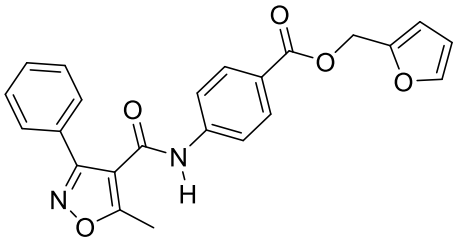
2-(Ethylthio)ethyl 4-(5-methyl-3-phenylisoxazole-4-carboxamido)benzoate (SI1)



Synthesis according to the General procedure VII. 4-(5-Methyl-3-phenylisoxazole-4-carboxamido)benzoic acid **12** (35.4 mg, 0.110 mmol), 2-(ethylthio)ethan-1-ol (57.2 µL 0.549 mmol, 5 equiv), HBTU (54.2 mg, 0.143 mmol, 1.3 equiv), DIPEA (38.3 µL, 0.220 mmol, 2 equiv), DMF (1 mL). Reaction time: 2 d. Solvent for extraction: diethyl ether

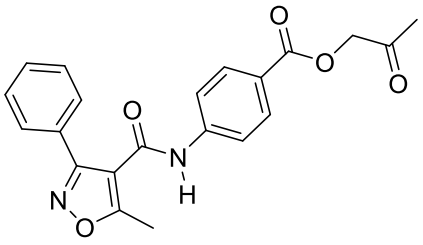
and water. Chromatography on silica gel gave compound **SI1** (38.7 mg, 0.0976 mmol, 89%) as a white solid. M.p. 109.8–110.4 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.72 (s, 1H), 7.94 (m$_c$, 2H), 7.75 (m$_c$, 2H), 7.70–7.62 (m, 2H), 7.52–7.42 (m, 3H), 4.38 (t, 2H, ^{3}J = 6.7 Hz), 2.86 (t, 2H, ^{3}J = 6.7 Hz), 2.58 (q, 2H, ^{3}J = 7.4 Hz), 2.58 (s, 3H), 1.18 (t, 3H, ^{3}J = 7.4 Hz) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 170.3, 165.0, 160.4, 160.2, 142.9, 130.3, 130.1, 128.8, 127.9, 127.7, 124.7, 119.1, 113.0, 63.7, 29.3, 25.2, 14.7, 11.9 ppm. HRMS calc. for $C_{22}H_{23}N_2O_4S$ [M+H]$^+$: 411.1379, found 411.1378.

Furan-2-ylmethyl 4-(5-methyl-3-phenylisoxazole-4-carboxamido)benzoate (SI2)



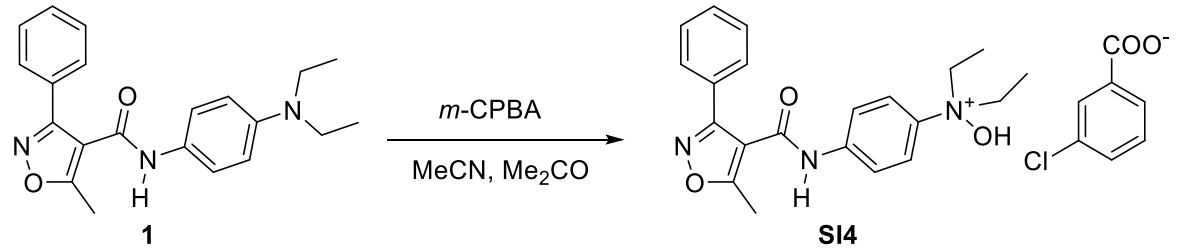
Synthesis according to the General procedure VII. 4-(5-Methyl-3-phenylisoxazole-4-carboxamido)benzoic acid **12** (32.2 mg, 0.100 mmol), furfurylalcohol (25.9 µL, 0.300 mmol, 3 equiv), HBTU (49.3 mg, 0.130 mmol, 1.3 equiv), DIPEA (34.8 µL, 0.200 mmol, 2 equiv), DMF (1 mL). Reaction time: 3 d. Solvent for extraction: diethyl ether and water. Chromatography on silica gel gave compound **SI12** (29.7 mg, 0.0738 mmol, 74%) as a white solid. M.p. 133.7–135.1 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.73 (s, 1H), 7.94 (m$_c$, 2H), 7.75 (m$_c$, 2H), 7.71 (dd, 1H, ^{4}J = 0.8 Hz, ^{3}J = 1.9 Hz), 7.70–7.63 (m, 2H), 7.53–7.44 (m, 3H), 6.60 (dd, 1H, ^{3}J = 3.3 Hz, ^{4}J = 0.8 Hz), 6.49 (dd, 1H, ^{3}J = 3.3 Hz, ^{3}J = 1.9 Hz), 5.30 (s, 2H), 2.59 (s, 3H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 170.3, 164.7, 160.3, 160.2, 149.3, 143.7, 143.0, 130.3, 130.1, 128.8, 127.9, 127.7, 124.4, 119.1, 112.9, 110.9, 110.7, 58.0, 11.9 ppm. HRMS calc. for $C_{23}H_{19}N_2O_5$ [M+H]$^+$: 403.1294, found 403.1299.

2-Oxopropyl 4-(5-methyl-3-phenylisoxazole-4-carboxamido)benzoate (SI3)



Synthesis according to the General procedure VII. Deviating from the General procedure VII, the chromatography was omitted and the product was recrystallized from MeOH. 4-(5-Methyl-3-phenylisoxazole-4-carboxamido)benzoic acid **12** (34.0 mg, 0.105 mmol), hydroxyacetone (21.7 µL, 0.316 mmol, 3 equiv), HBTU (51.8 mg, 0.137 mmol, 1.3 equiv), DIPEA (36.6 µL, 0.210 mmol, 2 equiv), DMF (1 mL). Reaction time: 2 d. Solvent for extraction: diethyl ether and water. Recrystallization gave compound **SI3** (28.5 mg, 0.0753 mmol, 72%) as a white solid. M.p. 199.9–201.5 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.76 (s, 1H), 7.99 (m$_c$, 2H), 7.78 (m$_c$, 2H), 7.72–7.65 (m, 2H), 7.53–7.45 (m, 3H), 4.99 (s, 2H), 2.60 (s, 3H), 2.16 ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 201.8, 170.3, 164.5, 160.4, 160.2, 143.1, 130.5, 130.1, 128.8, 127.9, 127.7, 124.1, 119.1, 113.0, 68.6, 25.9, 11.9 ppm. HRMS calc. for $C_{21}H_{19}N_2O_5$ [M+H]$^+$: 379.1294, found 379.1296.

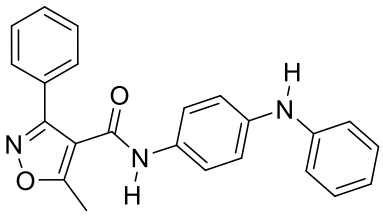
_N_,_N_-Diethyl-_N_-[4-(5-Methyl-3-phenylisoxazole-4-carboxamido)phenyl]hydroxylammonium 3-chlorobenzoate (SI4)



1 SI4

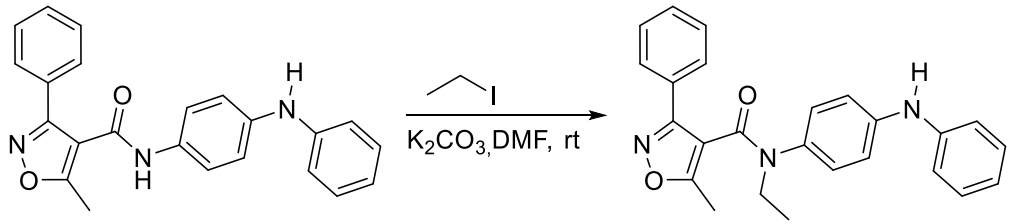
_N_-[4-(Diethylamino)phenyl]-5-methyl-3-phenylisoxazole-4-carboxamide **1** (349 mg, 1.00 mmol) was dissolved in a mixture of acetonitrile (5 mL) and acetone (3 mL). *m*-Chloroperoxybenzoic acid (77%, max, 288 mg, max. 1.28 mmol) was added to the solution. The reaction mixture was stirred for 30 min at room temperature, during which the product precipitated. Filtration gave compound **SI4** (371 mg, 0.711 mmol, 71%) as white needles. M.p. 139.7–141.8 °C (decomp.). ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.80 (s, 1H), 7.93–7.76 (m, 5H), 7.73–7.66 (m, 2H), 7.58–7.42 (m, 5H), 4.03 (q, 4H, ^{3}J = 7.0 Hz), 2.60 (s, 3H), 1.01 (t, 6H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 170.2, 167.6, 160.3, 141.3, 139.1, 137.3, 132.8, 130.9, 130.2, 130.0, 128.9, 128.8, 128.0, 127.8, 127.7, 122.4, 119.8, 113.1, 48.6, 12.0, 7.9 ppm. HRMS calc. for cation $C_{21}H_{24}N_3O_3$: 366.1809, found 366.1812.

5-Methyl-3-phenyl-_N_-[4-(phenylamino)phenyl]isoxazole-4-carboxamide (SI5)



Synthesis according to the General procedure I. The organic phase was washed twice with a mixture of water and brine (10:1). 5-Methyl-3-phenylisoxazole-4-carboxylic acid (1.00 g, 4.92 mmol), _N_-phenyl-_p_-phenylenediamine (1.09 g, 5.91 mmol, 1.2 equiv), HBTU (3.73 g, 9.84 mmol, 2 equiv), DIPEA (0.257 mL, 1.48 mmol, 3 equiv), DMF (20 mL). Deviating from the General procedure I, the automated chromatography started with 25% ethyl acetate in _n_-hexane and ended with 50% _n_-hexane in ethyl acetate. Recrystallization (MeOH/H_2O 10+1) after automated chromatography on silica gel gave compound **SI5** (1.00 g, 2.71 mmol, 55%) as fine white crystals. M.p. 142.9–146.5 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.27 (s, 1H), 8.09 (s, 1H), 7.76–7.68 (m, 2H), 7.54–7.47 (m, 5H), 7.24–7.17 (m, 2H), 7.09–6.99 (m, 4H), 6.81–6.75 (m, 1H), 2.58 (s, 3H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 169.6, 160.2, 159.4, 143.8, 139.6, 131.3, 130.1, 129.2, 128.8, 128.2, 127.7, 121.1, 119.2, 117.5, 116.0, 113.5, 11.9 ppm. HRMS calc. for $C_{23}H_{20}N_3O_2$ $[M+H]^+$: 370.1556, found 370.1558.

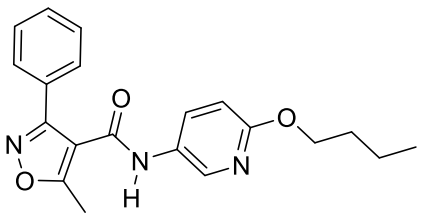
***N*-[4-[Ethyl(phenyl)amino]phenyl]-5-methyl-3-phenylisoxazole-4-carboxamide (SI6)**



SI5 **SI6**

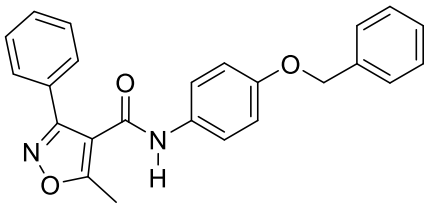
5-Methyl-3-phenyl-*N*-[4-(phenylamino)phenyl]isoxazole-4-carboxamide **SI5** (154 mg, 0.500 mmol) and potassium carbonate (104 mg, 0.750 mmol, 1.5 equiv) were dissolved in anhydrous DMF (3 mL) under argon and iodoethane (48.3 μL, 0.600 mmol, 1.2 equiv) was added to this solution. The reaction mixture was stirred for 2 d at room temperature. Diethyl ether was added, and the organic phase was washed three times with water. The organic solvents were removed with a rotary evaporator and the crude product was purified by automated chromatography on silica gel using a gradient of increasing ethyl acetate, starting with 100% *n*-hexane to yield compound **SI6** (47.0 mg, 0.118 mmol, 24%) as a colorless resin. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.14 (s, 1H), 7.58–7.45 (m, 5H), 7.27–7.19 (m, 2H), 7.03–6.96 (m, 2H), 6.87–6.81 (m, 1H), 6.78–6.70 (m, 2H), 6.57–6.48 (m, 2H), 3.76 (q, 2H, ^{3}J = 7.0 Hz), 2.36 (s, 3H), 1.09 (t, 3H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 168.1, 162.0, 159.3, 142.6, 142.4, 132.3, 130.1, 129.1, 128.8, 128.2, 128.2, 127.7, 127.0, 120.2, 117.2, 115.8, 111.7, 43.7, 12.5, 11.4 ppm. HRMS calc. for $C_{25}H_{24}N_3O_2$ $[M+H]^+$: 398.1869, found 398.1859.

***N*-(6-Butoxypyridin-3-yl)-5-methyl-3-phenylisoxazole-4-carboxamide (SI7)**



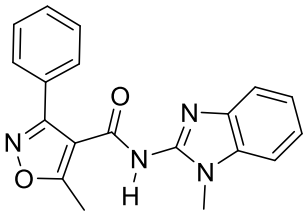
Synthesis according to the General procedure I. 5-Methyl-3-phenylisoxazole-4-carboxylic acid **6** (75.0 mg, 0.369 mmol), 5-amino-2-butoxypyridine hydrochloride (74.8 mg, 0.369 mmol), HBTU (0.210 g, 0.554 mmol, 1.5 equiv), DIPEA (0.257 mL, 1.48 mmol, 4 equiv), DMF (2 mL). Solvent for extraction: ethyl acetate. Recrystallization (MeOH) without chromatography on silica gel gave compound **SI7** (87.0 mg, 0.248 mmol, 67%) as white needles. M.p. 159.6–161.0 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.42 (s, 1H), 8.35 (d, 1H, J = 2.7 Hz), 7.90 (dd, 1H, J = 2.7 Hz, J = 8.9 Hz), 7.73–7.66 (m, 2H), 7.53–7.45 (m, 3H), 6.81 (d, 1H, J = 8.9 Hz), 4.22 (t, 2H, J = 6.6 Hz), 2.59 (s, 3H), 1.73–1.62 (m, 2H), 1.47–1.34 (m, 2H), 0.92 (t, 3H, J = 7.4 Hz) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 169.9, 160.1, 160.0, 159.9, 138.3, 132.0, 130.0, 129.0, 128.8, 127.9, 127.7, 112.9, 110.3, 65.1, 30.5, 18.7, 13.6, 11.9 ppm. HRMS calc. for $C_{20}H_{22}N_3O_3$ $[M+H]^+$: 352.1661, found 352.1664.

_N_-[4-(Benzyloxy)phenyl]-5-methyl-3-phenylisoxazole-4-carboxamide (SI8)



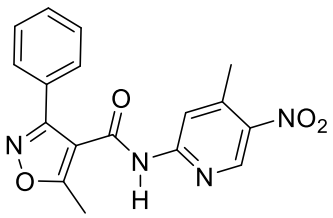
Synthesis according to the General procedure I. 5-Methyl-3-phenylisoxazole-4-carboxylic acid **6** (203 mg, 1.00 mmol), 4-(benzyloxy)aniline hydrochloride (236 mg, 1.00 mmol), HBTU (493 mg, 1.30 mmol, 1.3 equiv), DIPEA (0.523 mL, 2.00 mmol, 2 equiv), DMF (4 mL). Solvent for extraction: diethyl ether. Recrystallization (EtOH) without chromatography on silica gel gave compound **SI8** (289 mg, 0.751 mmol, 75%) as white needles. M.p. 155.1–157.3 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.26 (s, 1H), 7.74–7.67 (m, 2H), 7.56–7.29 (m, 10H), 7.00 (m_c, 2H), 5.09 (s, 2H), 2.57 (s, 3H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 169.6, 160.1, 159.5, 154.8, 137.0, 131.8, 130.0, 128.7, 128.3, 128.1, 127.7, 127.6, 127.5, 121.2, 114.9, 113.3, 69.3, 11.8 ppm. HRMS calc. for $C_{24}H_{21}N_2O_3$ $[M+H]^+$: 385.1552, found 385.1554.

5-Methyl-_N_-(1-methyl-1_H_-benzo[_d_]imidazol-2-yl)-3-phenylisoxazole-4-carboxamide (SI9)



Synthesis according to the General procedure I. 5-Methyl-3-phenylisoxazole-4-carboxylic acid **6** (203 mg, 1.00 mmol), 2-amino-1-methylbenzimidazole (147 mg, 1.00 mmol), HBTU (455 mg, 1.20 mmol, 1.2 equiv), DIPEA (0.348 mL, 2.00 mmol, 2 equiv), DMF (4 mL). Solvent for extraction: diethyl ether. Recrystallization (MeOH/H_2O 10+1) after chromatography on silica gel gave compound **SI9** (133 mg, 0.400 mmol, 40%) as white crystals. M.p. 156.7–158.4 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.55 (s, 1H), 7.68–7.68 (m, 2H), 7.51–7.39 (m, 5H), 7.73–7.66 (m, 2H), 7.27–7.16 (m, 2H), 3.38 (s, 3H), 2.84 (s, 3H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 172.6, 168.9, 162.5, 159.9, 151.7, 130.0, 129.7, 129.3, 128.8, 128.7, 127.7, 122.6, 122.5, 115.1, 111.9, 109.3, 27.9, 13.4 ppm. HRMS calc. for $C_{19}H_{17}N_4O_2$ $[M+H]^+$: 333.1352, found 333.1358.

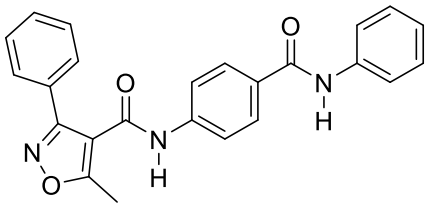
5-Methyl-_N_-(4-methyl-5-nitropyridin-2-yl)-3-phenylisoxazole-4-carboxamide (SI10)



Synthesis according to the General procedure II. Deviating from the General procedure II, the oxalyl chloride solution was stirred at room temperature for 1 h and DIPEA was added to the pyridine solution. 5-Methyl-3-phenylisoxazole-4-carboxylic acid **6** (508 mg, 2.50 mmol), 4-methyl-5-nitropyridin-2-amine (383 mg, 2.50 mmol), a 2 M solution of oxalyl chloride in DCM (3.13 mL, 6.25 mmol, 2.5 equiv), DMF (20.9 µL, 0.250 mmol, 0.1 equiv), DCM (5 mL), DIPEA (0.653 mL, 3.75 mmol, 1.5 equiv), pyridine (5 mL). Solvent for extraction: ethyl acetate. Recrystallization (MeOH/H_2O 20+1) after chromatography on silica gel gave compound **SI10** (72.0 mg, 0.213 mmol, 8.5%) as white needles. M.p. 174.4–175.3 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.46 (s, 1H), 8.99 (s, 1H), 8.22 (s, 1H), 7.67–7.60 (m, 2H), 7.53–7.45 (m, 3H), 2.62, 2.60 (s, 3H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 171.4, 161.3, 160.5,

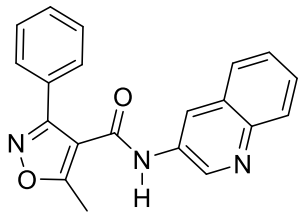
154.3, 145.8, 145.6, 141.7, 130.1, 128.9, 127.9, 127.9, 115.6, 112.3, 20.4, 12.2 ppm. HRMS calc. for $C_{17}H_{15}N_4O_4$ $[M+H]^+$: 339.1093, found 339.1100.

5-Methyl-3-phenyl-*N*-[4-(phenylcarbamoyl)phenyl]isoxazole-4-carboxamide (SI11)



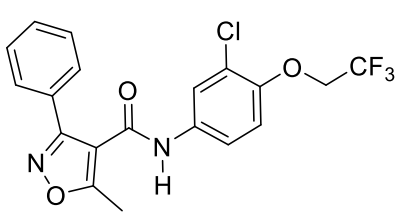
Synthesis according to the General procedure I. Deviating from the General procedure I, the ethyl acetate phase obtained from extraction was filtered, and the filtrate was purified by automated chromatography. The products obtained from chromatography and filtration were combined and recrystallized again (EtOAc/EtOH 1+1). 5-Methyl-3-phenylisoxazole-4-carboxylic acid **6** (406 mg, 2.00 mmol), 4-amino-*N*-phenylbenzamide (425 mg, 2.00 mmol), HBTU (986 mg, 2.60 mmol, 1.3 equiv), DIPEA (0.697 mL, 4.00 mmol, 2 equiv), DMF (5 mL). Solvent for extraction: ethyl acetate. Recrystallization (EtOH/EtOAc 11+1) after chromatography on silica gel gave compound **SI11** (0.220 g, 0.554 mmol, 28%) as a white solid. M.p. 248.4–249.6 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.79 (s, 1H), 10.19 (s, 1H), 8.04–7.97 (m, 2H), 7.84–7.75 (m, 4H), 7.74–7.66 (m, 2H), 7.54–7.45 (m, 3H), 7.39–7.29 (m, 2H), 7.13–7.05 (m, 1H), 2.62 (s, 3H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 170.1, 164.7, 160.2, 160.2, 141.4, 139.2, 130.0 130.0, 128.7, 128.6, 128.4, 128.0, 127.7, 123.4, 120.3, 118.9, 113.1, 69.4, 11.5 ppm. HRMS calc. for $C_{24}H_{20}N_3O_3$ $[M+H]^+$: 398.1505, found 398.1504.

5-Methyl-3-phenyl-*N*-(quinolin-3-yl)isoxazole-4-carboxamide (SI12)



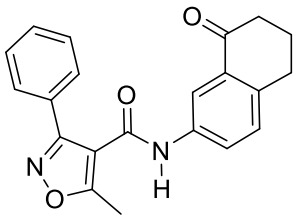
Synthesis according to the General procedure I. 5-Methyl-3-(2-nitrophenyl)isoxazole-4-carboxylic acid (203 mg, 1.00 mmol), 3-aminoquinoline (144 mg, 1.00 mmol), HBTU (493 mg, 1.30 mmol, 1.3 equiv), DIPEA (0.348 mL, 2.00 mmol, 2 equiv), DMF (3 mL). Solvent for extraction: ethyl acetate. Recrystallization (EtOH/H_2O 10+1) after chromatography on silica gel gave compound **SI12** (146 mg, 0.443 mmol, 44%) as white needles. M.p. 202.1–203.2 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.86 (s, 1H), 8.92 (d, 1H, ^4J = 2.5 Hz), 8.75 (d, 1H), 8.01–7.94 (m, 2H), 7.76–7.56 (m, 4H), 7.53–7.45 (m, 3H), 2.65 (s, 3H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 170.4, 160.7, 160.3, 144.6, 144.5, 132.2, 130.1, 128.8, 128.5, 128.2, 127.9, 127.8, 127.7, 127.6, 127.1, 123.1, 112.8, 12.0 ppm. HRMS calc. for $C_{20}H_{16}N_3O_2$ $[M+H]^+$: 330.1243, found 330.1246.

N-[3-Chloro-4-(2,2,2-trifluoroethoxy)phenyl]-5-methyl-3-phenylisoxazole-4-carboxamide (SI13)



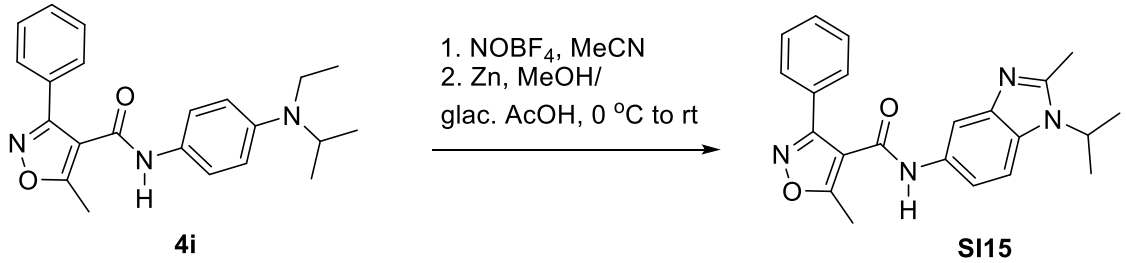
Synthesis according to the General procedure I. 5-Methyl-3-phenylisoxazole-4-carboxylic acid (21.3 mg, 0.105 mmol), 3-chloro-4-(2,2,2-trifluoroethoxy)aniline (23.6 mg, 0.105 mmol), HBTU (51.8 mg, 0.137 mmol, 1.3 equiv), DIPEA (36.6 μL, 0.210 mmol, 2 equiv), DMF (1 mL). Solvent for extraction: diethyl ether and water. Recrystallization (MeOH/H_2O 10+1) after chromatography on silica gel gave compound **SI13** (30.5 mg, 0.0742 mmol, 71%) as white needles. M.p. 166.4–168.4 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.48 (s, 1H), 7.83 (d, 1H, ^4J = 2.4 Hz), 7.72–7.64 (m, 2H), 7.54–7.42 (m, 4H), 7.28 (d, 1H, ^3J = 9.0 Hz), 4.82 (q, 2H, ^3J = 8.8 Hz), 2.59 (s, 3H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 170.0, 160.2, 159.9, 148.8, 133.8, 130.1, 128.8, 127.9, 127.7, 123.7 (d≈q, J = 278.4 Hz), 121.6, 121.3, 119.5, 115.5, 113.0, 65.8 (q, J = 34.3 Hz), 11.9 ppm. HRMS calc. for $C_{19}H_{15}ClF_3N_2O_3$ $[M+H]^+$: 411.0723, found 411.0723.

5-Methyl-*N*-(8-oxo-5,6,7,8-tetrahydronaphthalen-2-yl)-3-phenylisoxazole-4-carboxamide (SI14)



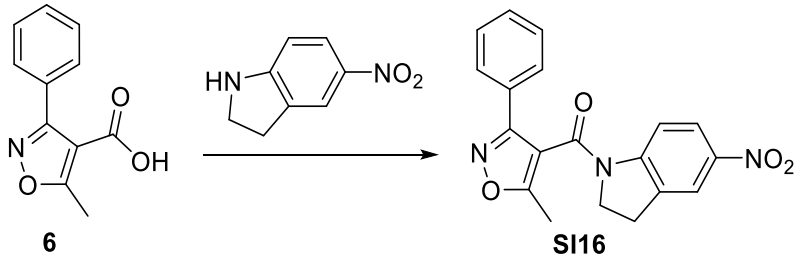
Synthesis according to the General procedure I. 5-Methyl-3-phenylisoxazole-4-carboxylic acid: (33.3 mg, 0.164 mmol), 7-amino-alpha-tetralone (26.4 mg, 0.164 mmol), HBTU (80.9 mg, 0.213 mmol, 1.3 equiv), DIPEA (57.1 μL, 0.328 mmol, 2 equiv), DMF (1 mL). Solvent for extraction: ethyl acetate and a mixture of water and brine (1:1). Recrystallization (MeOH/water 10+1) after chromatography on silica gel gave compound **SI14** (22.5 mg, 0.0650 mmol, 40%) as a brown solid. M.p. 176.5–178.2 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.78 (dd, 1H, ^4J = 2.4 Hz, ^3J = 8.3 Hz), 7.68–7.53 (m, 5H), 7.43 (d, 1H, ^4J = 2.4 Hz), 7.20 (d, 1H), 7.17 (s, 1H), 2.90 (t, 2H, J = 6.1 Hz), 2.60 (t, 2H, J = 7.1 Hz), 2.15–2.04 (m, 2H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 197.8, 175.5, 160.0, 140.9, 136.1, 133.1, 131.2, 129.8, 129.7, 129.3, 128.0, 125.5, 117.7, 111.3, 39.1, 29.3, 23.4, 13.3 ppm. HRMS calc. for $C_{21}H_{19}N_2O_3$ $[M+H]^+$: 347.1396, found 347.1404.

***N*-(1-Isopropyl-2-methyl-1*H*-benzo[*d*]imidazol-5-yl)-5-methyl-3-phenylisoxazole-4-carboxamide (SI15)**



Nitrosonium tetrafluoroborate (213 mg, 1.61 mmol) was dissolved in absolute acetonitrile (10 mL) and cooled to 0 °C in an ice bath. *N*-[4-[Ethyl(isopropyl)amino]phenyl]-5-methyl-3-phenylisoxazole-4-carboxamide **4i** (584 mg, 1.61 mmol) was added as a solid to the above-mentioned solution, and the reaction mixture was stirred for 2 h at 0 °C. Methanol (5 mL), glacial acetic acid (10 mL) and zinc powder (315 mg, 4.82 mmol) were added to the reaction mixture. The reaction mixture was stirred for 15 min at 0 °C and 6 h at room temperature. The reaction mixture was filtered through Celite® and the solvent was removed with a rotary evaporator. The residual acetic acid was removed by co-distillation with toluene with a rotary evaporator, and the solid residue was dissolved in ethyl acetate. Celite® was washed with methanol and water and the filtrate was combined with the ethyl acetate solution in a separatory funnel. The phases were separated, and the organic layer was washed several times with small portions of water until the aqueous phase remained neutral. The organic solvents were removed with a rotary evaporator, and the product mixture was purified by automated preparative chromatography. The chromatography on silica gel was performed with an increasing gradient of ethyl acetate in *n*-hexane, starting with 0% of ethyl acetate to give compound **SI15** (21.0 mg, 0.561 mmol, 3%) as a brownish solid. M.p. 200.2–202.7 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.34 (s, 1H), 7.86 (d, 1H, ^{3}J = 1.9 Hz), 7.76–7.68 (m, 2H), 7.60 (d, 1H, ^{3}J = 8.7 Hz), 7.55–7.43 (m, 3H), 7.32 (d, 1H), 4.70 (sept, 1H, ^{3}J = 6.9 Hz), 2.59 (s, 3H), 2.55 (s, 3H), 1.54 (d, 6H, J = 6.9 Hz) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ169.6, 160.1, 159.6, 151.9, 142.9, 132.4, 130.3, 130.1, 128.8, 128.2, 127.7, 114.5, 113.5, 111.3, 109.9, 47.3, 21.0, 14.4, 11.9 ppm. HRMS calc. for $C_{22}H_{23}FN_4$ $[M+H]^+$: 375.1821, found 375.1831.

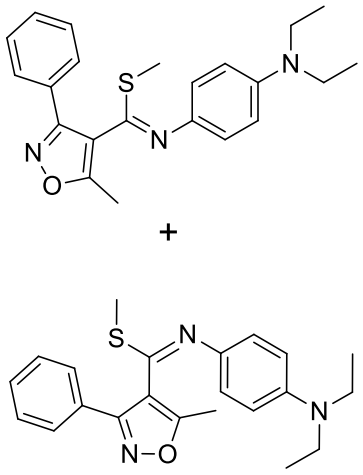
(5-Methyl-3-phenylisoxazol-4-yl)(5-nitroindolin-1-yl)methanone (SI16)



Synthesis according to the General procedure I. Deviating from the General procedure I, HATU, 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate, was used instead of HBTU and after the work-up, the ethereal phase was washed twice with water, 6 times with a small amount of 4 M hydrochloric acid and several times with water until the aqueous phase remained neutral. The crude product was recrystallized once from methanol and once from 2-propanol/ethyl acetate/MeOH (10+4+3). 5-Methyl-3-phenylisoxazole-4-carboxylic acid **6** (508 mg, 2.50 mmol), 5-nitroindoline (493 mg, 3.00 mmol, 1.2 equiv), HATU (1.14 g, 3.00 mmol, 1.2 equiv), DIPEA (1.31 mL, 7.50 mmol, 3 equiv), DMF (8 mL). Solvent for extraction: diethyl ether. Recrystallization (twice) [without chromatography on silica gel] gave compound **SI16** (339 mg, 0.970 mmol, 39%) as yellow crystals. M.p. 171.2–172.4 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.30–8.02 (m, 3H), 7.65–7.56 (m, 2H), 7.53–7.43 (m, 3H), 3.91 (bt, 2H), 3.09 (t, 2H, ^{3}J = 8.3 Hz), 2.56 (s, 3H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.5, 161.3, 159.4, 147.5, 143.4, 135.1, 130.5, 129.3, 127.8, 127.0 (2×), 124.2, 120.7, 111.9, 49.9, 26.8, 11.7 ppm. HRMS calc. for $C_{19}H_{16}N_3O_4$ $[M+H]^+$: 330.1494, found 330.1494.

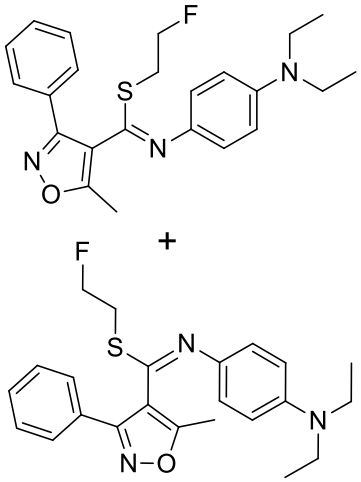
Preparation of compounds in Scheme 2 and other related compounds

(*E*) and (*Z*)-Methyl *N*-[4-(diethylamino)phenyl]-5-methyl-3-phenylisoxazole-4-carbimidothioate (24a)



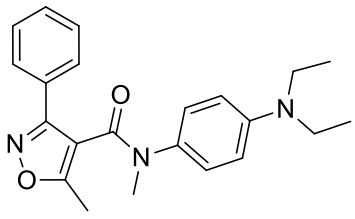
N-[4-(Diethylamino)phenyl]-5-methyl-3-phenylisoxazole-4-carbothioamide **23** (75.0 mg, 0.205 mmol) was dissolved in a mixture of acetonitrile (2.5 mL) and DMSO (2 mL). Lithium carbonate (22.7 mg, 0.308 mmol) and iodomethane (19.2 μL, 0.308 mmol) were added. The reaction mixture was heated at 38 °C overnight and diluted with ethyl acetate. The organic phase was washed three times with water. The solvent was removed with a rotary evaporator, and the crude product mixture was purified by automated preparative chromatography. The chromatography on silica gel was performed with an increasing gradient of ethyl acetate in *n*-hexane, starting with 0% of ethyl acetate to give compound **24a** (55.0 mg, 0.146 mmol, 71%) as a yellow oil. The ^{1}H NMR spectra show a mixture of isomers (**A** and **B**). The ratio of integrals is approximately 1:3, the isomer **B** being the minor one. The ^{13}C NMR spectra show only a few visible signals of the isomer **B**. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.79–7.72 (m, 2H, isomer **B**), 7.60–7.52 (m, 3H, isomer **B**), 7.50–7.38 (m, 5H), 6.83 (m_c, 2H, isomer **B**), 6.69 (m_c, 2H, isomer **B**), 6.40–6.30 (m, 4H), 3.33 (q, 4H, ^{3}J = 7.0 Hz, isomer **B**), 3.20 (q, 4H, ^{3}J = 7.0 Hz), 2.57 (s, 3H, isomer **B**), 2.51 (s, 3H), 2.39 (s, 3H), 1.95 (s, 3H, isomer **B**), 1.09 (t, 6H, isomer **B**), 1.00 (t, 6H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 168.4, 159.3, 154.4, 144.4 , 137.3, 129.9, 128.9, 128.7, 127.8, 127.4, 126.8, 121.8, 121.4, 111.8, 112.0, 111.7, 43.6, 13.4, 12.4, 12.3, 11.5 ppm. HRMS calc. for $C_{22}H_{26}N_3OS$ $[M+H]^+$: 380.1797, found 380.1801.

(*Z*) & (*E*)-2-Fluoroethyl *N*-[4-(diethylamino)phenyl]-5-methyl-3-phenylisoxazole-4-carbimidothioate (24b)



N-[4-(Diethylamino)phenyl]-5-methyl-3-phenylisoxazole-4-carbothioamide **23** (64.0 mg, 0.175 mmol) was dissolved in absolute DMF (2.5 mL) under argon. A 60% suspension of sodium hydride in mineral oil (8.4 mg, 0.210 mmol, 1.2 equiv) was added, and the reaction mixture was stirred for 2 h 0 °C. 1-Bromo-2-fluoroethane (15.7 μL, 0.210 mmol) was added, and the reaction mixture was stirred for 3 d at room temperature. The reaction mixture was diluted with ethyl acetate. The organic phase was washed three times with water. The solvent was removed with a rotary evaporator and the crude product mixture was purified by automated preparative chromatography. The chromatography on silica gel was performed with an increasing gradient of ethyl acetate in *n*-hexane, starting with 0% of ethyl acetate to give compound **24b** (56.8 mg, 0.138 mmol, 79%) as a yellow resin. The ^{1}H NMR spectra show a mixture of isomer **A** and isomer **B**. The ratio of integrals is approximately 1:4.6, with the isomer **B** being the minor one. In the ^{13}C NMR spectra only a few signals of the isomer **B** are visible. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.79–7.71 (m, 2H, isomer **B**), 7.60–7.51 (m, 3H, isomer **B**), 7.50–7.36 (m, 5H), 6.83 (m$_c$, 2H, isomer **B**), 6.70 (m$_c$, 2H, isomer **B**), 6.41–6.32 (m, 4H), 4.69 (dt, 2H, ^{2}J = 47.2 Hz, ^{3}J = 6.1 Hz), 4.26 (dt, 2H, ^{2}J = 47.1 Hz, ^{3}J = 5.7 Hz), 3.60 (m, 2H), 3.33 (q, 4H, ^{3}J = 7.0 Hz, isomer **B**), 3.21 (q, 4H, ^{3}J = 7.0 Hz), 2.81 (dt, 2H', ^{3}J = 24.1 Hz, ^{3}J = 5.7 Hz, isomer **B**), 2.58 (s, 3H, isomer **B**), 2.40 (s, 3H), 1.10 (t, 6H, isomer **B**), 1.00 (t, 6H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 168.7, 159.3, 152.2, 144.6, 136.8, 130.0, 128.8, 128.7, 127.6, 126.8, 122.0, 121.4, 111.7, 111.7, 109.5, 81.3 (d, ^{1}J = 167.5 Hz), 43.6, 29.7 (d, $^{2}J_{HF}$ = 21.5 Hz), 12.2, 11.4 ppm. HRMS calc. for $C_{23}H_{27}FN_3OS$ $[M+H]^+$: 412.1859, found 412.1859.

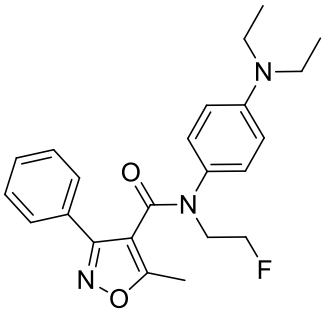
***N*-[4-(Diethylamino)phenyl]-*N*,5-dimethyl-3-phenylisoxazole-4-carboxamide (25a)**



N-[4-(Diethylamino)phenyl]-5-methyl-3-phenylisoxazole-4-carboxamide **1**, (175 mg, 0.500 mmol) was dissolved in anhydrous DMF (2.5 mL) under argon, cooled to 0 °C in an ice bath, and a 60% dispersion of sodium hydride in mineral oil (30.0 mg, 0.750 mmol, 1.5 equiv) was added. After 1 h, iodomethane (37.4 μL, 0.600 mmol, 1.2 equiv) was added. The ice bath was removed, and the reaction mixture was stirred at room temperature for 4 d. Water and ethyl acetate were added, the phases were separated, and the organic phase was washed twice with water. The organic solvents were removed with a rotary evaporator, and the crude product was purified by automated chromatography on silica gel using a gradient of increasing ethyl acetate, starting with 100% *n*-hexane to yield compound **25a** (139 mg, 0.382 mmol, 76%) as a white solid. M.p. 88.9–93.3 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.56–7.43 (m, 5H), 6.51 (m$_c$, 2H), 6.32 (m$_c$, 2H), 3.25 (s, 3H), 3.23 (q, 4H, ^{3}J = 7.0 Hz), 2.33 (s, 3H), 1.01 (t, 6H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 168.0, 162.4, 159.4, 145.9, 130.3, 129.9, 128.7,

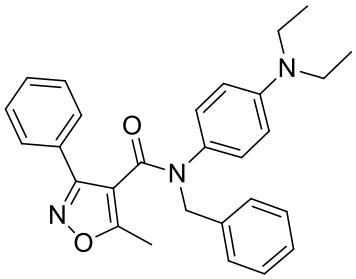
128.3, 127.0, 126.7, 112.8, 111.0, 43.6, 37.1, 12.2, 11.4 ppm. HRMS calc. for $C_{22}H_{26}N_3O_2$ $[M+H]^+$: 364.2025, found 364.2025.

N-[4-(Diethylamino)phenyl]-*N*-(2-fluoroethyl)-5-methyl-3-phenylisoxazole-4-carboxamide (25b)



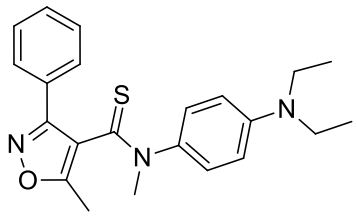
N-[4-(Diethylamino)phenyl]-5-methyl-3-phenylisoxazole-4-carboxamide **1** (175 mg, 0.500 mmol) was dissolved in absolute DMF (2.5 mL) under argon. A 60% suspension of sodium hydride in mineral oil (24.0 mg, 0.600 mmol, 1.2 equiv) was added, and the reaction mixture was stirred for 2 h at room temperature. 1-Bromo-2-fluoroethane (56.0 μL, 0.750 mmol, 1.5 equiv) was added, and the reaction mixture was stirred overnight at room temperature. The reaction mixture was diluted with diethyl ether. The organic phase was washed three times with water. The solvent was removed with a rotary evaporator, and the crude product mixture was purified by automated preparative chromatography. The chromatography on silica gel was performed with an increasing gradient of ethyl acetate in *n*-hexane, starting with 0% of ethyl acetate to give compound **25b** (157 mg, 0.397 mmol, 79%) as a colorless oil. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.56–7.44 (m, 5H), 6.54 (m_c, 2H), 6.32 (m_c, 2H), 4.57 (dt, 2H, ^2J = 47.5 Hz, ^3J = 5.0 Hz), 4.03 (dt, 2H, ^3J = 26.2 Hz, ^3J = 5.0 Hz), 3.23 (q, 4H, ^3J = 7.0 Hz), 2.33 (s, 3H), 1.01 (t, 6H, ^3J = 7.0 Hz) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 167.8, 163.1, 159.2, 146.2, 130.0, 128.8, 128.4, 128.2, 127.7, 127.0, 112.8, 110.9, 80.7 (d, ^1J = 167.0 Hz), 49.2 (d, ^2J = 20.2 Hz), 43.5, 12.2, 11.4 ppm. HRMS calc. for $C_{23}H_{27}FN_3O_2$ $[M+H]^+$: 396.2087, found 396.2084.

N-Benzyl-*N*-[4-(diethylamino)phenyl]-5-methyl-3-phenylisoxazole-4-carboxamide (25c)



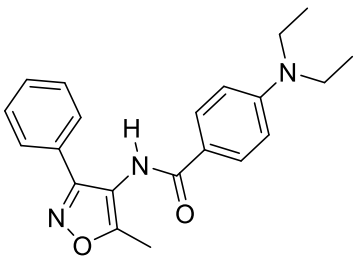
N-[4-(Diethylamino)phenyl]-5-methyl-3-phenylisoxazole-4-carboxamide **1** (0.100 g, 0.286 mmol) was dissolved in anhydrous DMF (2.5 mL) under argon and cooled to 0 °C. A 60% dispersion of sodium hydride in mineral oil (13.7 mg, 0.343 mmol, 1.2 equiv) was added. After 1.5 h, benzyl bromide (0.102 mL, 0.858 mmol, 3 equiv) was added. The cooling bath was removed after 2 h, and the reaction mixture was stirred at room temperature overnight. Ethyl acetate was added, and the organic phase was washed three times with a mixture of water and brine (3:1). The organic solvents were removed with a rotary evaporator, and the crude product was purified by automated chromatography on silica gel using a gradient of increasing ethyl acetate, starting with 100% *n*-hexane to yield compound **25c** (102 mg, 0.232 mmol, 81%) as white crystals. M.p. 129.8-133.0 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.55–7.40 (m, 5H), 7.34–7.19 (m, 5H), 6.35 (m_c, 2H), 6.23 (m_c, 2H), 4.93 (bs, 2H), 3.18 (q, 4H, J = 7.0 Hz), 2.36 (s, 3H), 0.97 (t, 6H, J = 7.0 Hz) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 167.8, 162.9, 159.4, 146.1, 137.2, 130.0, 128.7, 128.4 , 128.3, 128.2, 128.1, 127.6, 127.2, 127.1, 112.8, 110.7, 52.3, 43.4, 12.2, 11.5 ppm. HRMS calc. for $C_{28}H_{30}N_3O_2$ $[M+H]^+$: 440.2338, found 440.2338.

N-[4-(Diethylamino)phenyl]-*N*,5-dimethyl-3-phenylisoxazole-4-carbothioamide (26)



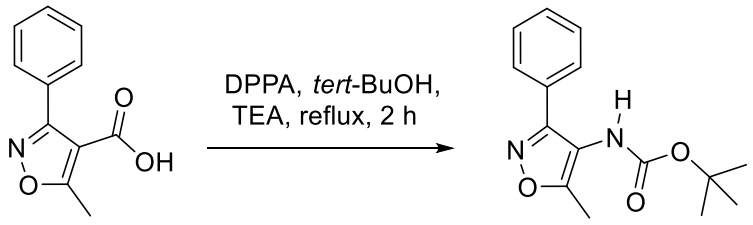
Synthesis according to the General procedure V. Deviating from the General procedure V, the solvent of the reaction mixture was removed with a rotary evaporator prior chromatography without purification by extraction. *N*-[4-(Diethylamino)phenyl]-*N*,5-dimethyl-3-phenylisoxazole-4-carboxamide **25a** (50.0 mg, 0.138 mmol), Lawesson's reagent (33.4 mg, 0.0825 mmol, 0.6 equiv), toluene (1 mL). Reaction time: 8 h. Chromatography on silica gel gave compound **26** (44.5 mg, 0.117 mmol, 85%) as a yellow solid. M.p. 126.5–127.7 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.54–7.43 (m, 3H), 7.42–7.36 (m, 2H), 6.35 (m$_c$, 2H), 6.26 (m$_c$, 2H), 3.69 (s, 3H), 3.23 (m, 4H), 2.43 (s, 3H), 1.00 (t, 6H, ^{3}J = 7.0 Hz) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 188.8, 167.1, 157.2, 146.2, 132.5, 129.8, 128.6, 128.4, 126.9, 125.3, 119.4, 110.6, 45.0, 43.6, 12.1, 11.3 ppm. HRMS calc. for $C_{22}H_{26}N_3OS$ $[M+H]^+$: 380.1797, found 380.1799.

4-(Diethylamino)-*N*-(5-methyl-3-phenylisoxazol-4-yl)benzamide (27)



Synthesis according to the General procedure II. 4-(Diethylamino)benzoic acid **29** (111 mg, 0.574 mmol), a 2 M solution of oxalyl chloride in DCM (1.72 mL, 3.44 mmol, 6 equiv), 5-methyl-3-phenylisoxazol-4-amine **28** (0.100 g, 0.574 mmol), DCM (1 mL), pyridine (2 mL). Recrystallization (MeOH/H_2O 10+1) after chromatography on silica gel gave compound **27** (70.0 mg, 0.200 mmol, 35%) as white crystals. M.p. 189.8–191.0 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.47 (s, 1H), 7.80 (m$_c$, 2H), 7.75–7.68 (m, 2H), 7.49–7.43 (m, 3H), 6.70 (m$_c$, 2H), 3.41 (q, 4H, ^{3}J = 7.0 Hz), 2.34 (s, 3H), 1.12 (t, 6H, ^{3}J = 7.0 Hz) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 165.9, 165.9, 159.4, 149.9, 129.7, 129.4, 128.7, 128.4, 127.0, 118.7, 113.4, 110.1, 43.7, 12.3, 10.7 ppm. HRMS calc. for $C_{21}H_{24}N_3O_2$ $[M+H]^+$: 350.1869, found 350.1874.

tert-Butyl (5-methyl-3-phenylisoxazol-4-yl)carbamate (SI17)

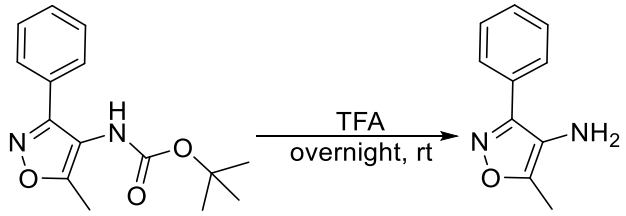


6 **SI17**

5-Methyl-3-phenylisoxazole-4-carboxylic acid **6** (8.00 g, 39.4 mmol) was dissolved in *tert*-butanol (70 mL) under argon. Triethylamine (5.49 mL, 39.4 mmol) and diphenylphosphoryl azide (8.51 mL,

39.4 mmol) were added, and the reaction mixture was heated at reflux temperature for 2 h. After cooling to room temperature, ethyl acetate was added and the organic phase was washed three times with water. The combined aqueous phases were extracted once with ethyl acetate and the combined ethyl acetate phases were washed twice with a 1 M solution of sodium hydroxide in water and with small portions of water until the aqueous phase remained neutral. The organic solvents were removed with a rotary evaporator and recrystallized twice (MeOH/H_2O 10+1). The solvent of the mother liquor was removed with a rotary evaporator, and the residue was purified by automated chromatography on silica gel with an increasing gradient of ethyl acetate in *n*-hexane, starting with 0% of ethyl acetate. The combined material from crystallizations and chromatography was recrystallized (MeOH/H_2O 10+1) to give compound **SI17** (6.77 g, 24.7 mmol, 63%) as white needles. M.p. 116.8–119.9 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.72–7.65 (m, 2H), 7.54–7.40 (m, 3H), 5.65 (bs, 1H), 2.41 (s, 3H), 1.56 (bs, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.88, 159.43, 154.14, 129.92, 128.95, 128.66, 127.74, 112.87, 81.28, 28.27, 11.28 ppm. HRMS calc. for $C_{15}H_{19}N_2O_3$ $[M+H]^+$: 275.1396, found 275.1396.

5-Methyl-3-phenylisoxazol-4-amine (28)



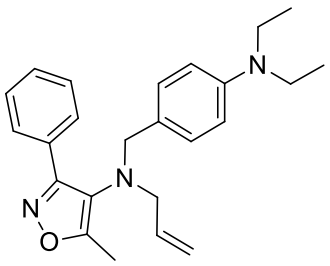
SI17 **28**

A solution of *tert*-butyl (5-methyl-3-phenylisoxazol-4-yl)carbamate **SI17** (5.259 g, 19.17 mmol) in trifluoroacetic acid (20 mL) was stirred at room temperature overnight. Diethyl ether and water were added and the resulting solution was made basic with a 10 M solution of sodium hydroxide in water. Phases were separated and the aqueous phase was extracted with diethyl ether. The organic phase was washed three times with water and the solvent was removed with the rotary evaporator. The resulting crude product mixture was subjected to a purification by an automated high performance flash chromatography (*n*-hexane/EtOAc 0→100%) to yield 5-methyl-3-phenylisoxazol-4-amine **28** (1.728 g, 9.92 mmol, 52%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.99–7.75 (m, 2H), 7.54–7.40 (m, 3H), 3.96 (s, 1H), 2.34 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 155.69, 153.39, 129.44, 129.08, 128.65, 128.65, 127.15, 121.96, 9.88. HRMS calc. for $C_{10}H_{11}N_2O$ $[M+H]^+$: 175.0871, found 175.0891.

***N*-Allyl-*N*-[4-(diethylamino)benzyl]-5-methyl-3-phenylisoxazol-4-amine (30b)**

A mixture of *N*-[4-(diethylamino)benzyl]-5-methyl-3-phenylisoxazol-4-amine **33** (23.0 mg, 0.0686 mmol), allyl iodide (7.50 μL, 0.0823 mmol, 1.2 equiv) and cesium carbonate (31.3 mg, 0.0960 mmol, 1.4 equiv) in absolute DMF (0.20 mL) was stirred for 3 d at room temperature under argon. The

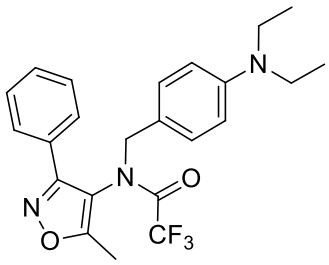
reaction mixture was diluted with ethyl acetate and washed three times with water. The solvent was removed with a rotary evaporator, and the crude product was subjected to automated preparative chromatography. The chromatography on silica gel was performed with an increasing gradient of ethyl acetate in *n*-hexane, starting with 0% of ethyl acetate to give compound **30b** (12.1 mg, 0.0322 mmol, 47%) as a brownish oil.



^{1}H NMR (300 MHz, $CDCl_3$): δ 8.00–7.92 (m, 2H), 7.48–7.39 (m, 3H), 6.96 (m_c, 2H), 6.58 (m_c, 2H), 5.83 (ddt, 1H, ^3J = 6.4 Hz, ^3J = 10.3 Hz, ^3J = 17.1 Hz), 5.17–5.06 (m, 2H), 3.91 (s, 2H), 3.58-3.47 (m, 2H), 3.33 (q, 4H, ^3J = 7.0 Hz), 2.18 (s, 3H), 1.14 (t, 6H, ^3J = 7.0 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.8, 160.0, 147.4, 135.5, 130.4, 130.1, 129.4, 128.5, 128.1, 125.4, 124.3, 117.6, 111.9, 57.1, 55.6, 44.5, 12.7, 12.3 ppm. HRMS calc. for $C_{24}H_{30}N_3O$ $[M+H]^+$: 376.2389, found 376.2386.

_N_-[4-(Diethylamino)benzyl]-2,2,2-trifluoro-_N_-(5-methyl-3-phenylisoxazol-4-yl)acetamide (30c)

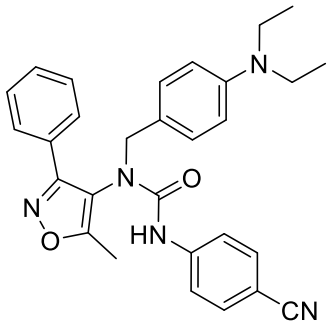
A mixture of *N*-[4-(diethylamino)benzyl]-5-methyl-3-phenylisoxazol-4-amine **33** (20.7 mg, 0.0617 mmol), trifluoroacetic anhydride (13.1 μL, 0.0926 mmol, 1.5 equiv) and DMAP (11.3 mg, 0.0926 mmol, 1.5 equiv) in absolute pyridine (0.30 mL) was stirred for 2 d at room temperature under argon. The reaction mixture was diluted with ethyl acetate and washed once with a saturated solution of sodium hydrogen carbonate in water and twice with water. The solvent was removed with a rotary evaporator and the crude product was subjected to automated preparative chromatography. The chromatography on silica gel was performed with an increasing gradient of ethyl acetate in *n*-hexane, starting with 0% of ethyl acetate to give compound **30c** (16.9 mg, 0.0392 mmol, 63%) as a yellowish oil.



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.76–7.69 (m, 2H), 7.53–7.43 (m, 3H), 6.95 (m_c, 2H), 6.54 (m_c, 2H), 5.50 (d, 1H, ^3J = 13.6 Hz), 3.69 (d,1H), 3.33 (q, 4H, ^3J = 7.0 Hz), 1.70 (s, 3H), 1.14 (t, 6H, ^3J = 7.0 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.3, 158.4, 157.8 (q, J = 35.2 Hz), 148.2, 131.4, 130.6, 129.3, 127.6, 127.0, 120.6, 116.2 (q, J = 288.6 Hz), 113.9, 111.9, 53.6, 44.5, 12.6, 10.2 ppm. HRMS calc. for $C_{23}H_{25}F_3N_3O_2$ $[M+H]^+$: 432.1899, found 432.1899.

3-(4-Cyanophenyl)-1-[4-(diethylamino)benzyl)]-1-(5-methyl-3-phenylisoxazol-4-yl)urea (30d)

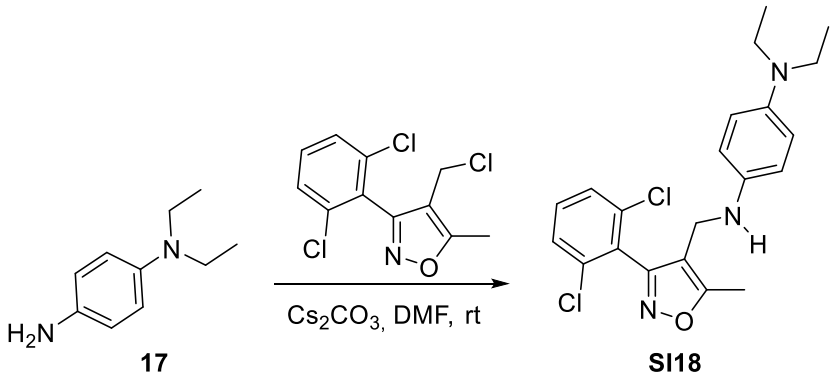
A mixture of *N*-[4-(diethylamino)benzyl]-5-methyl-3-phenylisoxazol-4-amine **33** (21.7 mg, 64.7 μmol) and 4-isocyanatobenzonitrile (10.3 mg, 0.0712 mmol, 1.1 equiv) in absolute THF (0.30 mL) was stirred for 4 d at room temperature under argon. The solvent was removed with a rotary evaporator, and the crude product was subjected to automated preparative chromatography. The chromatography on silica gel was performed with an increasing gradient of ethyl acetate in *n*-hexane, starting with 0% of ethyl acetate to give compound **30d** (25.3 mg, 0.0528 mmol, 82%) as a white solid. M.p. 199.2–201.7 °C.



^{1}H NMR (300 MHz,

DMSO-d_6): δ 8.84 (s, 1H), 7.70–7.63 (m, 4H), 7.58–7.50 (m, 2H), 7.50–7.41 (m, 3H), 6.90 (m_c, 2H), 6.51 (m_c, 2H), 5.00 (d, 1H, ^2J = 14.0 Hz), 3.83 (d, 1H), 3.27 (q, 4H, ^3J = 7.0 Hz), 1.88 (s, 3H), 1.04 (t, 6H, ^3J = 7.0 Hz) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 168.0, 158.7, 154.0, 147.0, 144.3, 132.5, 130.3, 129.9, 128.9, 127.8, 126.7, 122.7, 120.0, 119.1, 115.3, 111.3, 103.8, 51.1, 43.5, 12.2, 10.2 ppm. HRMS calc. for $C_{29}H_{29}N_5O_2$ $[M+H]^+$: 480.2400, found 480.2400.

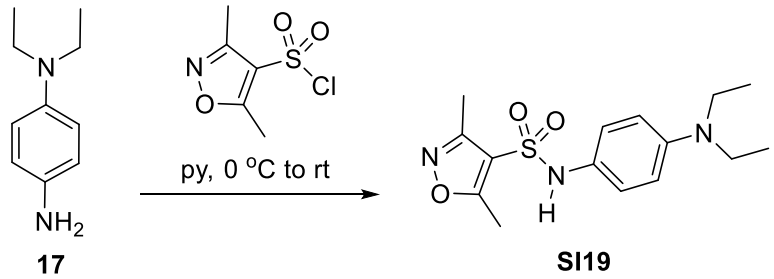
N^1-[(3-(2,6-Dichlorophenyl)-5-methylisoxazol-4-yl)methyl]-N^4,N^4-diethylbenzene-1,4-diamine (SI18)



17 **SI18**

4-(Chloromethyl)-3-(2,6-dichlorophenyl)-5-methylisoxazole (86.5 mg, 0.313 mmol) was dissolved under argon in absolute DMF (2 mL). *N*,*N*-diethyl-*p*-phenylenediamine **17** (78.0 µL, 0.469 mmol, 1.5 equiv) and cesium carbonate (163 mg, 0.501 mmol, 1.6 equiv) were added, and the reaction mixture was shaken for 4 d at room temperature. The reaction mixture was diluted with ethyl acetate and washed three times with a mixture of water and brine (3:1). The solvent was removed with a rotary evaporator, and the crude product was subjected to automated preparative chromatography. The chromatography on silica gel was performed with an increasing gradient of ethyl acetate in *n*-hexane, starting with 0% of ethyl acetate gave compound **SI18** (66.4 mg, 0.164 mmol, 52%) as a red-brown oil. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.63–7.50 (m, 3H), 6.52, 6.36 (each m_c, each 2H), 4.88 (t, 1H, ^3J = 5.8 Hz), 3.80 (d, 2H, ^3J = 5.8 Hz), 3.09 (q, 4H, ^3J = 7.0 Hz), 2.48 (s, 3H), 1.95 (t, 6H, ^3J = 7.0 Hz) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 167.2, 158.7, 140.2, 140.1, 134.6, 132.2, 128.4, 127.4, 116.3, 113.7, 113.2, 44.8, 36.9, 12.3, 11.1 ppm. HRMS calc. for $C_{21}H_{24}Cl_2N_3O$ $[M+H]^+$: 404.1296, found 404.1292.

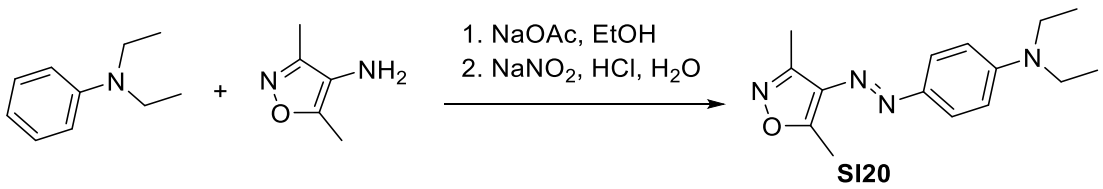
***N*-[4-(Diethylamino)phenyl]-3,5-dimethylisoxazole-4-sulfonamide (SI19)**



17 **SI19**

N,*N*-Diethyl-*p*-phenylenediamine **17** (63.5 µL, 0.382 mmol) was dissolved in anhydrous pyridine (3 mL) under argon and cooled to 0 °C. 3,5-Dimethylisoxazole-4-sulfonyl chloride (74.7 mg, 0.382 mmol) was added. After 30 min the ice bath was removed, and the reaction mixture was stirred at room temperature overnight. Pyridine was removed by co-distillation with toluene (3 × 20 mL) with a rotary evaporator. Automated chromatography on silica gel starting with 100% *n*-hexane and ending after an increasing gradient with 100% ethyl acetate gave compound **SI19** (81.0 mg, 0.250 mmol, 66%) as brownish resin. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.60 (s, 1H), 6.83 (m_c, 2H), 6.59 (m_c, 2H), 3.28 (q, 4H, ^{3}J = 7.0 Hz), 2.28, 2.13 (s, 3H), 1.04 (t, 6H, ^{3}J = 7.0 Hz) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 172.7, 157.3, 146.0, 125.9, 123.5, 115.2, 111.9, 43.6, 12.1 11.8, 10.2 ppm. HRMS calc. for $C_{15}H_{22}N_3O_3S$ $[M+H]^+$: 324.1382, found 324.1391.

(*E*)-4-[(3,5-Dimethylisoxazol-4-yl)diazenyl]-*N*,*N*-diethylaniline (SI20)

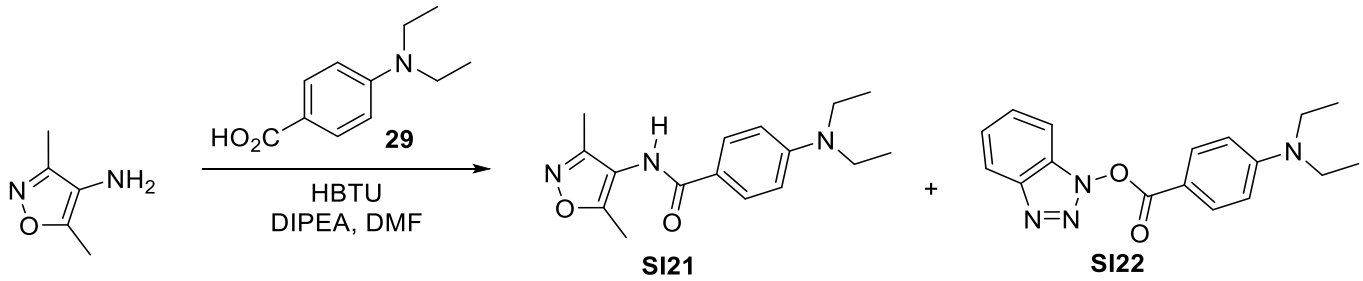


SI20

N,*N*-Diethylaniline (112 mg, 1.00 mol) was dissolved in ethanol (3 mL). To this solution, sodium acetate (0.410 g, 5.00 mmol, 5 equiv) was added, and the solution was cooled to 0 °C in an ice bath. A solution of sodium nitrite (69.0 mg, 1.00 mmol) in water (0.5 mL) was prepared and cooled to 0 °C. 3,5-Dimethylisoxazol-4-amine (112 mg, 1.00 mol) was dissolved in an equimixture of concentrated hydrochloric acid and water (1 mL) and cooled to 0 °C in an ice bath. To this solution, the sodium nitrite solution was added slowly during a period of 20 min. The reaction mixture was stirred for another 20 min, and the resulting mixture was added during a period of 7 min to the *N*,*N*-diethylaniline solution. The reaction mixture was stirred for 2 h. Diethyl ether was added, and the organic phase was washed once with a 0.5 M solution of sodium hydroxide in water and twice with water. The organic solvents were removed with a rotary evaporator, and the crude product was purified by automated chromatography on silica gel using a gradient of increasing ethyl acetate, starting with 100% *n*-hexane. The product was recrystallized from MeOH/H_2O (20+1) to yield

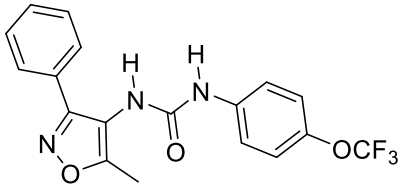
compound **SI20** (54.0 mg, 0.198 mmol, 20%) as orange crystals. M.p. 92.5–95.0 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.67 (m_c, 2H), 6.77 (m_c, 2H), 3.44 (q, 4H, ^{3}J = 7.0 Hz), 2.67 (s, 3H), 2.43 (s, 3H), 1.14 (t, 6H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 166.1, 153.4, 149.8, 142.4, 131.5, 124.3, 110.9, 44.0, 12.5 11.7, 11.3 ppm. HRMS calc. for $C_{15}H_{21}N_4O$ $[M+H]^+$: 273.1715, found 273.1715.

4-(Diethylamino)-*N*-(3,5-dimethylisoxazol-4-yl)benzamide (SI21) and 1*H*-benzo[*d*][1,2,3]triazol-1-yl 4-(diethylamino)benzoate (SI22)



Synthesis according to the General procedure I. 4-(Diethylamino)benzoic acid **29** (431 mg, 2.23 mmol), 3,5-dimethylisoxazol-4-amine (0.250 g, 2.23 mmol), HBTU (1.27 g, 3.35 mmol, 1.5 equiv), DIPEA (0.583 mL, 3.35 mmol, 1.5 equiv), DMF (5 mL). Solvent for extraction: ethyl acetate. Recrystallization (MeOH/H_2O 10+1) after chromatography on silica gel gave compound **SI21** (0.140 g, 0.487 mmol, 22%) as white needles. In addition, 1*H*-benzo[*d*][1,2,3]triazol-1-yl 4-(diethylamino)benzoate **SI22**, (0.200 g, 0.644 mmol, 29%) could be isolated as yellow needles. **SI21** : M.p. 170.5–180.3 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.30 (s, 1H), 7.81 (m_c, 2H), 6.70 (m_c, 2H), 3.41 (q, 4H, ^{3}J = 7.0 Hz), 2.27 (s, 3H), 2.10 (s, 3H), 1.12 (t, 6H, ^{3}J = 7.0 Hz) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 165.4, 162.3, 157.9, 149.8 , 129.4, 118.8, 114.8, 110.1, 43.7, 12.3 10.8, 9.5 ppm. HRMS calc. for $C_{16}H_{22}N_3O_2$ $[M+H]^+$: 288.1712, found 288.1714. **SI22**: M.p. 140.0–141.4 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.15 (dt, 1H, ^{3}J = 8.4 Hz, ^{4}J = 1.0 Hz), 8.01 (m_c, 2H), 7.78 (dt, 1H, ^{3}J = 8.4 Hz, ^{4}J = 1.0 Hz), 7.65 (ddd, 1H, $^{3}J_{5,6}$= 6.9 Hz), 7.52 (ddd, 1H), 6.87 (m_c, 2H), 3.50 (q, 4H, ^{3}J = 7.0 Hz), 1.17 (t, 6H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 167.4, 158.2, 151.0, 144.5, 130.9, 128.7, 127.8, 127.0, 126.3, 121.9, 112.9, 111.7, 43.7, 12.3 ppm. HRMS calc. for $C_{17}H_{19}N_4O_2$ $[M+H]^+$: 311.1503, found 311.1506.

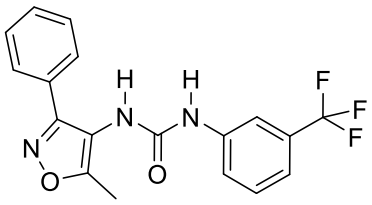
1-(5-Methyl-3-phenylisoxazol-4-yl)-3-[4-(trifluoromethoxy)phenyl]urea (SI23)



Synthesis according to the General procedure IV. Deviating from the General procedure IV, the reaction mixture was stirred at room temperature for 3 d. Then *n*-hexane (2 mL) was added dropwise, the formed precipitate was filtered and recrystallized (MeOH/H_2O 10+1). 5-Methyl-3-phenylisoxazol-4-amine **28** (86.3 mg, 0.495 mmol), 4-trifluoromethoxyphenyl isocyanate (74.7 µL, 0.495

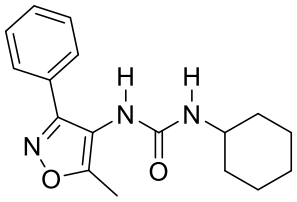
mmol), toluene (2 mL). Recrystallization gave compound **SI23** (0.110 g, 0.291 mmol, 59%) as white crystals. M.p. 161.2–162.4 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.12 (bs, 1H), 7.93 (bs, 1H), 7.78–7.70 (m, 2H), 7.56–7.47 (m, 5H), 7.25 (m$_c$, 2H), 2.37 (s, 3H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 166.2, 159.4, 153.7, 142.6, 139.1, 129.9, 128.9, 128.3, 127.3, 121.7, 120.2 (J = 266.5 Hz), 119.5, 113.2, 10.8 ppm. HRMS calc. for $C_{18}H_{15}F_3N_3O_3$ $[M+H]^+$: 378.1066 found 378.1063.

1-(5-Methyl-3-phenylisoxazol-4-yl)-3-[3-(trifluoromethyl)phenyl]urea (SI24)



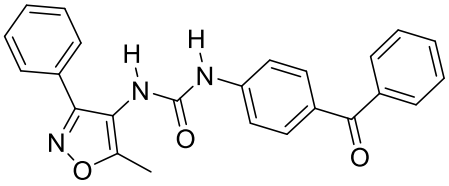
Synthesis according to the General procedure IV. Deviating from the General procedure IV, the reaction mixture was stirred at room temperature for 4 d. 5-Methyl-3-phenylisoxazol-4-amine **28** (158 mg, 0.907 mmol), 3-(trifluoromethyl)phenyl isocyanate (0.127 mL, 0.907 mmol), toluene (2 mL). For recrystallization of the reaction mixture, toluene (3 mL) was added and ethyl acetate (1-2 mL) was added in small portions until the precipitate was soluble in the hot solution. This gave compound **SI24** (271 mg, 0.750 mmol, 83%) as a white solid. M.p. 177.0–177.8 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.22 (bs, 1H, NH), 7.99 (bs, 1H), 7.93 (bs, 1H), 7.79–7.71 (m, 2H), 7.65–7.59 (m, 1H), 7.55–7.43 (m, 4H), 7.31–7.25 (m, 1H), 2.38 (s, 3H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 166.2, 159.3, 153.7, 140.6, 129.8, 129.7, 129.3 (q, J = 11.2 Hz), 128.7, 128.2, 127.1, 124.1 (q, J = 272.0 Hz), 121.9, 118.0 (q, J = 3.9 Hz), 114.3 (q, J = 4.0 Hz), 113.0, 10.7 ppm. HRMS calc. for $C_{18}H_{15}F_3N_3O_2$ $[M+H]^+$: 362.1116, found 362.1116.

1-Cyclohexyl-3-(5-methyl-3-phenylisoxazol-4-yl)urea (SI25)



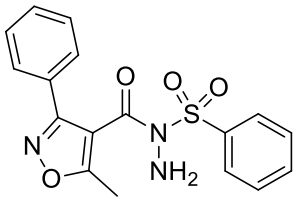
Synthesis according to the General procedure IV. Deviating from the General procedure IV, toluene was removed with a rotary evaporator, and the crude product was recrystallized (EtOH/H_2O 10+1). 5-Methyl-3-phenylisoxazol-4-amine **28** (105 mg, 0.603 mmol), cyclohexyl isocyanate (77.0 μL, 0.603 mmol), toluene (2 mL). Recrystallization (EtOH/H_2O 10+1) gave compound **SI25** (107 mg, 0.357 mmol, 59%) as white needles. M.p. 181.3–182.6 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.73–7.66 (m, 2H), 7.53–7.44 (m, 3H), 7.36 (s, 1H), 6.16 (d, 1H, ^{3}J = 8.1 Hz), 3.45–3.32 (m, 1H), 2.30 (s, 3H), 1.78–1.46 (m, 5H), 1.35–1.05 (m, 5H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 165.6, 159.3, 155.5, 129.6, 128.6, 128.5, 127.1, 113.9, 48.1, 32.9, 25.2, 24.4, 10.7 ppm. HRMS calc. for $C_{17}H_{22}N_3O_2$ $[M+H]^+$: 300.1712, found 300.1716.

1-(4-Benzoylphenyl)-3-(5-methyl-3-phenylisoxazol-4-yl)urea (SI26)



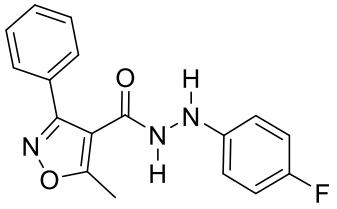
Synthesis according to the General procedure IV. 5-Methyl-3-phenylisoxazol-4-amine **28** (0.110 g, 0.631 mmol), 4-isocyanatobenzophenone (141 mg, 0.631 mmol), toluene (2 mL). Automated chromatography on silica gel gave compound **SI26** (98.0 mg, 0.247 mmol, 39%) as a white solid. M.p. 187.1–192.9 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.36 (s, 1H), 8.01 (s, 1H), 7.78–7.48 (m, 14H), 2.39 (s, 3H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 194.3, 166.1, 159.3, 153.4, 144.2, 137.7, 132.0, 131.2, 130.0, 129.8, 129.2, 128.8, 128.4, 128.2, 127.2, 117.3, 113.0, 10.8 ppm. HRMS calc. for $C_{24}H_{20}N_3O_3$ $[M+H]^+$: 398.1505, found 398.1505.

***N*-(5-Methyl-3-phenylisoxazole-4-carbonyl)benzenesulfonohydrazide (SI27)**



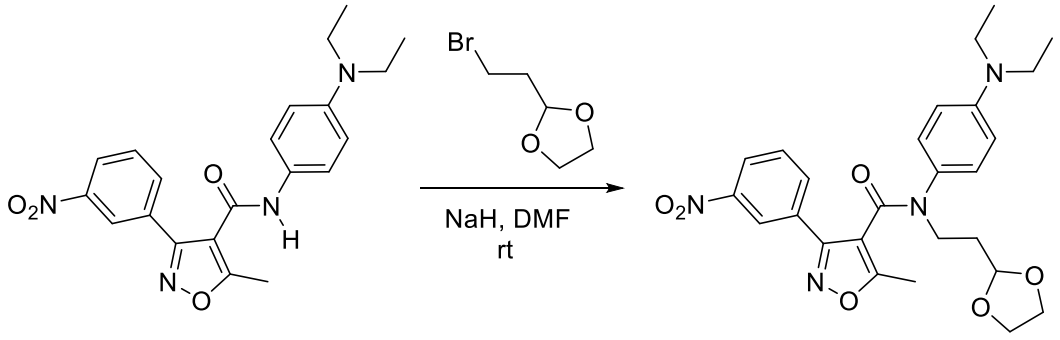
Synthesis according to the General procedure I. 5-Methyl-3-phenylisoxazole-4-carboxylic acid **6** (406 mg, 2.00 mmol), benzenesulfonohydrazide (344 mg, 2.00 mmol), HBTU (986 mg, 2.60 mmol, 1.3 equiv), DIPEA (0.697 mL, 4.00 mmol, 2 equiv), DMF (5 mL). Solvent for extraction: ethyl acetate/diethyl ether (1+1). Recrystallization (EtOH) after chromatography on silica gel gave compound **SI27** (233 mg, 0.652 mmol, 33%) as white crystals. M.p. 128.8–130.7 °C (decomp.). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.08–8.01 (m, 2H), 7.85–7.77 (m, 1H), 7.72–7.64 (m, 2H), 7.48–7.41 (m, 1H), 7.35–7.23 (m, 4H), 5.81 (s, 2H), 2.46 (s, 3H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 170.1, 163.9, 160.3, 137.7, 134.2, 130.0, 128.9, 128.7, 128.5, 127.7, 127.1, 111.0, 12.1 ppm. HRMS calc. for $C_{17}H_{16}N_3O_4S$ $[M+H]^+$: 358.0862, found 358.0861.

***N*'-(4-Fluorophenyl)-5-methyl-3-phenylisoxazole-4-carbohydrazide (SI28)**



Synthesis according to the General procedure I. Deviating from the General procedure I, the reaction time was 2 d. 5-Methyl-3-phenylisoxazole-4-carboxylic acid, (203 mg, 1.00 mmol), (4-fluorophenyl)hydrazine hydrochloride (162 mg, 1.00 mmol), HBTU (493 mg, 1.30 mmol, 1.3 equiv), DIPEA (0.523 mL, 3.00 mmol, 3 equiv), DMF (3 mL). Solvent for extraction: ethyl acetate. Recrystallization ($EtOH/H_2O$ 10+1) after chromatography on silica gel gave compound **SI28** (97.3 mg, 0.313 mmol, 31%) as fine white needles. M.p. 195.7–196.4 °C (decomp.). ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.18 (s, 1H), 7.96 (s, 1H), 7.72–7.64 (m, 2H), 7.57–7.45 (m, 3H), 7.00 (m_c, 2H), 6.79–6.69 (m, 2H), 2.61 (s, 3H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 169.7, 161.5, 160.4, 155.9 (d, J = 233.9 Hz), 145.4, 130.0, 128.7, 128.0, 127.8, 115.2 (d, J = 22.4 Hz), 113.5 (d, J = 7.7 Hz), 111.2, 11.9 ppm. HRMS calc. for $C_{17}H_{15}FN_3O_2$ $[M+H]^+$: 312.1148, found 312.1154.

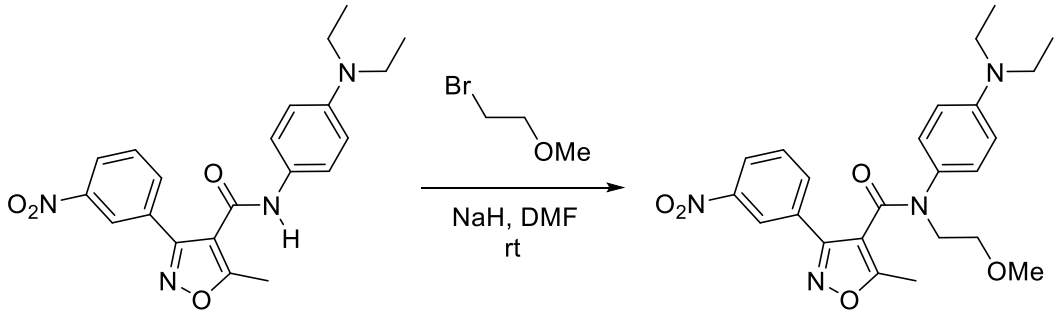
***N*-[2-(1,3-Dioxolan-2-yl)ethyl]-*N*-[4-(diethylamino)phenyl]-5-methyl-3-(3-nitrophenyl)isoxazole-4-carboxamide (SI29)**



39g **SI29**

N-[4-(Diethylamino)phenyl]-5-methyl-3-(3-nitrophenyl)isoxazole-4-carboxamide **39g** (75.0 mg, 0.190 mmol) was dissolved in absolute DMF (1 mL) under argon. A 60% suspension of sodium hydride in mineral oil (9.90 mg, 0.247 mmol, 1.3 equiv) was added, and the reaction mixture was stirred for 2 h at room temperature. 2-(2-Bromoethyl)-1,3-dioxolane (29.6 µL, 0.247 mmol, 1.3 equiv) was added, and the reaction mixture was stirred overnight at room temperature. A small amount of methanol and water was added. Diethyl ether was added and the organic phase was washed three times with water. The solvent was removed with a rotary evaporator, and the crude product was purified by automated preparative chromatography. The chromatography on silica gel was performed with an increasing gradient of ethyl acetate in *n*-hexane, starting with 0% of ethyl acetate to give compound **SI29** (59.5 mg, 0.120 mmol, 63%) as a brownish orange resin. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.29–8.23 (m, 2H), 7.88 (ddd≈ddt, 1H, ^{3}J = 7.7 Hz, ^{4}J = 1.4 Hz, ^{4}J = 1.4 Hz), 7.56 (dd, 1H, ^{3}J = 8.9 Hz), 6.32 (m_c, 2H), 6.17 (m_c, 2H), 4.93 (t, 1H, ^{3}J = 4.6 Hz), 3.96–3.74 (m, 6H), 3.19 (q, 4H, ^{3}J = 7.1 Hz), 2.45 (s, 3H), 1.94 (m_c, 2H), 1.06 (t, 6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.2, 163.0, 158.4, 148.4, 146.7, 133.7, 131.0, 129.7, 128.5, 127.9, 124.5, 122.9, 113.5, 111.1, 103.0, 65.1, 45.4, 44.5, 32.0, 12.6, 12.3 ppm. HRMS calc. for $C_{26}H_{31}N_4O_6$ $[M+H]^+$: 495.2244, found 495.2244.

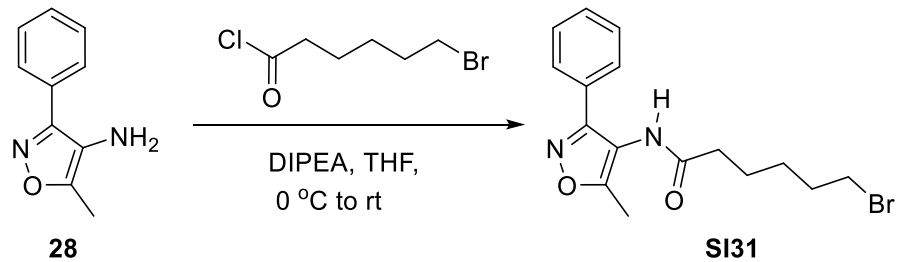
_N_-[4-(Diethylamino)phenyl]-_N_-(2-methoxyethyl)-5-methyl-3-(3-nitrophenyl)isoxazole-4-carboxamide (SI30)



39g **SI30**

_N_-[4-(Diethylamino)phenyl]-5-methyl-3-(3-nitrophenyl)isoxazole-4-carboxamide **39g** (75.0 mg, 0.190 mmol) was dissolved in absolute DMF (1 mL) under argon. A 60% suspension of sodium hydride in mineral oil (9.90 mg, 0.247 mmol, 1.3 equiv) was added, and the reaction mixture was stirred for 2 h at room temperature. 1-Bromo-2-methoxyethane (23.2 µL, 0.247 mmol, 1.3 equiv) was added and the reaction mixture was stirred overnight at room temperature. A small amount of methanol and water was added. Then diethyl ether was added, and the organic phase was washed three times with water. The solvent was removed with a rotary evaporator, and the crude product was purified by automated preparative chromatography. The chromatography on silica gel was performed with an increasing gradient of ethyl acetate in _n_-hexane, starting with 0% of ethyl acetate to give compound **SI30** (53.3 mg, 0.118 mmol, 62%) as a brownish orange resin. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.31 (dd≈t, 1H, ^{4}J = 1.8 Hz, ^{4}J = 1.8 Hz), 8.26 (ddd, 1H, ^{3}J = 8.2 Hz, ^{4}J = 1.1 Hz), 7.88 (ddd≈ddt, 1H, ^{3}J = 7.7 Hz), 7.56 (dd≈t, 1H), 6.42 (m_c, 2H), 6.19 (m_c, 2H), 3.95 (t, 2H, ^{3}J = 5.6 Hz), 3.56 (t, 2H, ^{3}J = 5.6 Hz), 3.33 (s, 3H), 3.22 (q, 4H, ^{3}J = 7.1 Hz), 2.44 (s, 3H), 1.06 (t, 6H, ^{3}J = 7.1 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ170.1, 163.5, 158.5, 148.5, 146.7, 133.9, 130.9, 129.7, 128.9, 127.9, 124.4, 122.9, 113.5, 111.0, 69.2, 58.9, 49.5, 44.5, 12.6, 12.3 ppm. HRMS calc. for $C_{24}H_{29}N_4O_5$ $[M+H]^+$: 453.2138, found 453.2139.

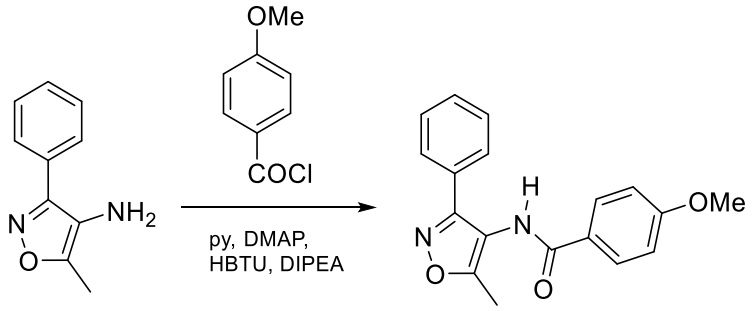
6-Bromo-_N_-(5-methyl-3-phenylisoxazol-4-yl)hexanamide (SI31)



28 **SI31**

5-Methyl-3-phenylisoxazol-4-amine **28** (211 mg, 1.00 mmol) and DIPEA (0.522 mL, 3.00 mmol) were dissolved in anhydrous THF (5 mL) and cooled to 0 °C. 6-Bromohexanoyl chloride (0.224 mL, 1.50 mmol) was added, and the reaction mixture was stirred overnight, while it was allowed to warm to rt. Diethyl ether was added, and the organic phase was washed with water, twice with a 2 M solution of sodium hydroxide in water, twice with 2 M hydrochloric acid solution and several times with water until the aqueous phase remained neutral. The organic solvents were removed with a rotary evaporator, and the crude product was purified by automated chromatography on silica gel using an increasing gradient of diethyl ether in *n*-hexane, starting with 0% of diethyl ether to yield compound **SI31** (291 mg, 0.828 mmol, 83%) as a white solid. M.p. 79.4–82.1 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ9.41 (s, 1H), 7.71–7.64 (m, 2H), 7.53–7.47 (m, 3H,), 2.64 (t, 2H, ^{3}J = 7.6 Hz), 3.52 (t, 2H, ^{3}J = 6.7 Hz), 2.34–2.27 (m, 5H), 1.87–1.74 (m, 2H), 1.65–1.53 (m, 2H), 1.45–1.33 (m, 2H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ172.3, 165.8, 159.0, 129.9, 128.9, 128.2, 127.2, 112.8, 35.1, 35.0, 31.9, 27.2, 24.2, 10.8 ppm. HRMS calc. for $C_{16}H_{20}BrN_2O_2$ [M+H]$^+$: 351.0708, found 351.0705.

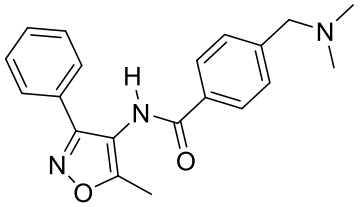
4-Methoxy-*N*-(5-methyl-3-phenylisoxazol-4-yl)benzamide (SI32)



28 **SI32**

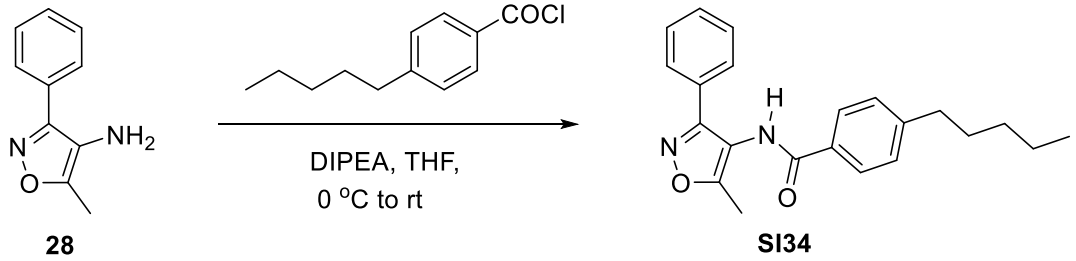
5-Methyl-3-phenylisoxazol-4-amine, **28** (105 mg, 0.500 mmol) was dissolved in anhydrous pyridine (2 mL) under argon and cooled to 0 °C. Anisoyl chloride (102 mg, 0.600 mmol) was added, and the reaction mixture was stirred overnight while it was allowed to warm to rt. DMAP (61.1 mg, 0.500 mmol) was added, and the reaction mixture was stirred overnight. HBTU (189 mg, 0.500 mmol) and DIPEA (0.261 mL, 1.50 mmol) were added, and the reaction mixture was stirred overnight. Diethyl ether was added, and the organic phase was washed with water, twice with a 2 M solution of sodium hydroxide in water, twice with 2 M hydrochloric acid and several times with water until the aqueous phase remained neutral. The organic solvents were removed with a rotary evaporator, and the crude product was purified by automated preparative chromatography on silica gel with an increasing gradient of ethyl acetate in *n*-hexane, starting with 0% of ethyl acetate to yield compound **SI32** (28 mg, 0.091 mmol, 18%) as a white solid. M.p. 150.4–155.4 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.78 (s, 1H), 7.95 (m$_c$, 2H), 7.75–7.68 (m, 2H), 7.50–7.43 (m, 3H,), 7.06 (m$_c$, 2H), 3.84 (s, 3H), 2.36 (s, 3H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ166.0, 165.6, 162.1, 159.3, 129.8, 129.5, 128.8, 128.3, 127.0, 125.4, 113.7 113.3, 55.4, 10.7 ppm. HRMS calc. for $C_{18}H_{17}N_2O_3$ [M+H]$^+$: 309.1239, found 309.1237.

4-[(Dimethylamino)methyl]-*N*-(5-methyl-3-phenylisoxazol-4-yl)benzamide (SI33)



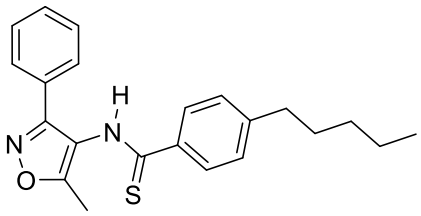
Synthesis according to the General procedure I. Deviating from the General procedure I, the reaction mixture was first stirred at room temperature for 4 d and then heated at 70 °C for 5 h. For the work-up ethyl acetate was added and the organic phase was washed twice with a 0.5 M solution of sodium hydroxide in water and once with water. 4-[(Dimethylamino)methyl]benzoic acid (52.2 mg, 0.291 mmol), 5-methyl-3-phenylisoxazol-4-amine **28** (50.7 mg, 0.291 mmol), HBTU (144 mg, 0.378 mmol, 1.3 equiv), DIPEA (0.101 mL, 0.582 mmol, 2 equiv), DMF (2 mL). Solvent for extraction: ethyl acetate. Automated chromatography on silica gel gave compound **SI33** (37.0 mg, 0.110 mmol, 38%) as a brownish solid. M.p. 101.5–105.3 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.90 (s, 1H), 7.92 (m$_c$, 2H), 7.75–7.68 (m, 2H), 7.51–7.40 (m, 5H), 3.46 (s, 2H), 2.37 (s, 3H), 2.16 (s, 6H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 166.1, 166.1, 159.3, 143.3, 131.9, 129.8, 128.8, 128.6, 128.3, 127.5, 127.0, 112.9, 62.9, 44.9, 10.7 ppm. HRMS calc. for $C_{20}H_{22}N_3O_2$ $[M+H]^+$: 336.1712, found 336.1717.

***N*-(5-Methyl-3-phenylisoxazol-4-yl)-4-pentylbenzamide (SI34)**



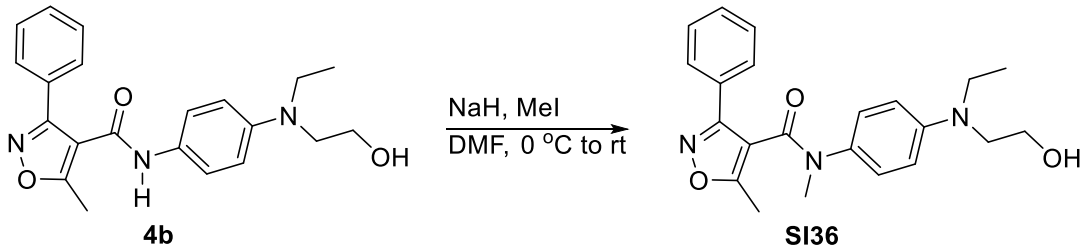
5-Methyl-3-phenylisoxazol-4-amine **28** (105 mg, 0.500 mmol) and DIPEA (0.261 mL, 1.50 mmol) were dissolved in anhydrous THF (3 mL) and cooled to 0 °C. 4-Pentylbenzoyl chloride (0.153 mL, 0.750 mmol) was added, the ice bath was removed after 30 min and the reaction mixture was stirred overnight at room temperature. Diethyl ether was added and the organic phase was washed with water, twice with a 2 M solution of sodium hydroxide ion water, twice with 2 M hydrochloric acid and several times with water until the aqueous phase remained neutral. The solvent was removed with a rotary evaporator, and the crude product was recrystallized (MeOH/H_2O 10+1) to yield compound **SI34** (128 mg, 0.367 mmol, 73%) as fine white crystals. M.p. 97.7–99.2 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.90 (s, 1H), 7.88 (m$_c$, 2H), 7.75–7.68 (m, 2H), 7.52–7.44 (m, 3H,), 7.35 (m$_c$, 2H), 2.64 (t, 2H, ^{3}J = 7.6 Hz), 2.36 (s, 3H), 1.60 (m$_c$), 1.37–1.21 (m, 4H), 0.86 (t, 3H, J = 6.9 Hz) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 166.2, 166.2, 159.3, 146.9, 130.7, 129.9, 128.9, 128.5, 128.3, 127.7, 127.0, 113.0, 34.9, 30.8, 30.4, 21.9, 13.9, 10.8 ppm. HRMS calc. for $C_{22}H_{25}N_2O_2$ $[M+H]^+$: 349.1916, found 349.1916.

N-(5-Methyl-3-phenylisoxazol-4-yl)-4-pentylbenzothioamide (SI35)



Synthesis according to the General procedure V. Deviating from the General procedure V, the solvent of the reaction mixture was removed with a rotary evaporator prior chromatography without purification by extraction. *N*-(5-Methyl-3-phenylisoxazol-4-yl)-4-pentylbenzamide **SI34** (45.0 mg, 0.129 mmol), Lawesson's reagent (31.3 mg, 77.5 μmol, 0.6 equiv), toluene (1 mL). Reaction time: 7 h. Chromatography on silica gel gave compound **SI35** (40.8 mg, 0.112 mmol, 87%) as a yellow solid. M.p. 136.7–137.7 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.31 (s, 1H), 7.85 (m$_c$, 2H), 7.72–7.64 (m, 2H), 7.53–7.45 (m, 3H), 7.31 (m$_c$, 2H), 2.64 (t, 2H, ^{3}J = 7.6 Hz), 2.36 (s, 3H), 1.60 (m$_c$, 2H), 1.40–1.22 (m, 4H), 0.87 (t, 3H, J = 6.8 Hz) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 200.7, 166.2, 158.9, 146.5, 137.6, 130.0, 128.9, 128.0, 127.5, 126.8, 116.0, 34.8, 30.7, 30.2, 21.8, 13.8, 11.0 ppm. HRMS calc. for $C_{22}H_{25}N_2OS$ $[M+H]^+$: 365.1688, found 365.1692.

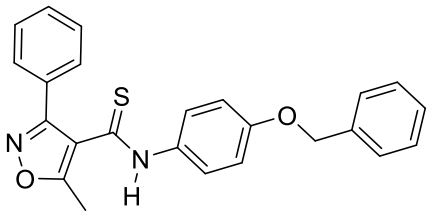
N-[4-[Ethyl(2-hydroxyethyl)amino]phenyl]-*N*,5-dimethyl-3-phenylisoxazole-4-carboxamide (SI36)



4b **SI36**

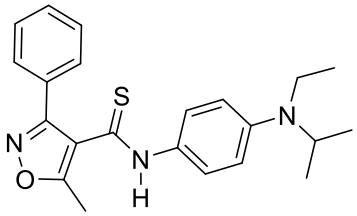
N-[4-[Ethyl(2-hydroxyethyl)amino]phenyl]-5-methyl-3-phenylisoxazole-4-carboxamide **4b** (70.0 mg, 0.192 mmol) was dissolved in absolute DMF (2 mL) and cooled to 0 °C in an ice bath. To this solution a dispersion of sodium hydride in mineral oil (17.6 mg, 0.441 mmol) was added, and the reaction mixture was stirred for 1.5 h at 0 °C. Iodomethane (12.0 μL, 0.192 mmol) was added, and the reaction mixture was stirred for 2 h at 0 °C and overnight at room temperature. Another portion of a dispersion of sodium hydride in mineral oil (17.6 mg, 0.441 mmol) was added, and the reaction mixture was stirred for 2 h at room temperature. Iodomethane (12.0 μL, 0.192 mmol) was added and the reaction mixture was stirred overnight at room temperature. A small amount of water was added slowly, and the resulting mixture was diluted with ethyl acetate and washed three times with water. The solvent was removed with a rotary evaporator, and the crude product was purified by automated chromatography on silica gel, using an increasing gradient of ethyl acetate in *n*-hexane, starting with 0% of ethyl acetate to give compound **SI36** (54 mg, 0.142 mmol, 74%) as a slightly yellow resin. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.58–7.42 (m, 5H), 6.50 (m$_c$, 2H), 6.34 (m$_c$, 2H), 4.61 (t, 1H, ^{3}J = 5.4 Hz), 3.51 (q, 2H, ^{3}J = 5.8Hz), 3.32–3.17 (m, 7H), 2.33 (s, 3H), 1.00 (t, 3H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 167.9, 162.4, 159.4, 146.2, 130.3, 129.9, 128.7, 128.3, 127.0, 126.6, 112.8, 110.9, 58.2, 52.0, 44.5, 44.5, 37.1, 11.7, 11.4 ppm. HRMS calc. for $C_{22}H_{26}N_3O_3$ $[M+H]^+$: 380.1974, found 380.1986.

_N_-[4-(Benzyloxy)phenyl]-5-methyl-3-phenylisoxazole-4-carbothioamide (SI37)



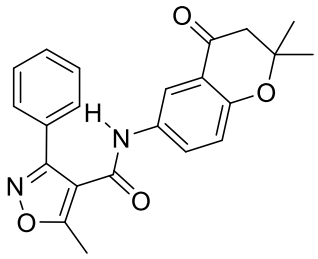
Synthesis according to the General procedure V. _N_-[4-(benzyloxy)phenyl]-5-methyl-3-phenylisoxazole-4-carboxamide **SI8** (130 mg, 0.338 mmol), Lawesson's reagent (82.1 mg, 0.203 mmol, 0.6 equiv), toluene (2.5 mL). Reaction time: overnight. Recrystallization from ethanol after chromatography on silica gel gave compound **SI37** (112 mg, 0.280 mmol, 83%) as small yellow needles. M.p. 153.3–158.2 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.86 (s, 1H), 7.75–7.63 (m, 4H), 7.55–7.28 (m, 8H), 7.06 (m_c, 2H), 5.12 (s, 2H), 2.53 (s, 3H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 186.3, 167.7, 158.8, 156.5, 136.9, 132.3, 130.0, 128.8, 128.5, 128.1, 127.9, 127.6, 127.5, 124.6, 114.7, 109.6, 69.4, 11.5 ppm. HRMS calc. for $C_{24}H_{21}N_2O_2S$ $[M+H]^+$: 401.1324, found 401.1326.

_N_-[4-[Ethyl(isopropyl)amino]phenyl]-5-methyl-3-phenylisoxazole-4-carbothioamide (SI38)



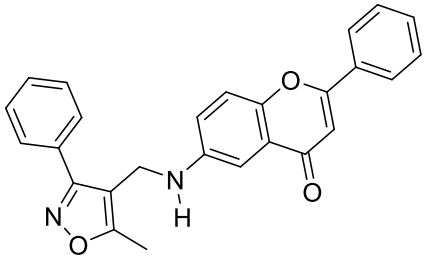
Synthesis according to the General procedure V. 4-[Ethyl(isopropyl)amino]-_N_-(5-methyl-3-phenylisoxazol-4-yl)benzamide **4i** (162 mg, 0.446 mmol), Lawesson's reagent (108 mg, 0.267 mmol, 0.6 equiv), toluene (3 mL). Reaction time: overnight. Recrystallization (EtOAc/EtOH 3+2) after chromatography on silica gel gave compound **SI38** (92.0 mg, 0.242 mmol, 54%) as fine yellow needles. M.p. 221.8–223.4 °C (decomp.). ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.68 (s, 1H), 7.74–7.65 (m, 2H), 7.60 (m_c, 2H), 7.53–7.42 (m, 3H), 6.72 (m_c, 2H), 4.05 (sept, 1H, ^{3}J = 6.6 Hz), 3.23 (q, 2H, ^{3}J = 7.0 Hz), 2.51 (s, 3H), 1.14 (d, 6H), 1.09 (t, 3H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 184.0, 167.2, 158.6, 146.5, 129.8, 128.6, 128.1, 127.7, 127.4, 123.9, 111.5, 110.7, 47.5, 37.2, 19.8, 14.6, 11.3 ppm. HRMS calc. for $C_{22}H_{26}N_3OS$ $[M+H]^+$: 380.1797, found 380.1796.

N-(2,2-Dimethyl-4-oxochroman-6-yl)-5-methyl-3-phenylisoxazole-4-carboxamide (SI39)



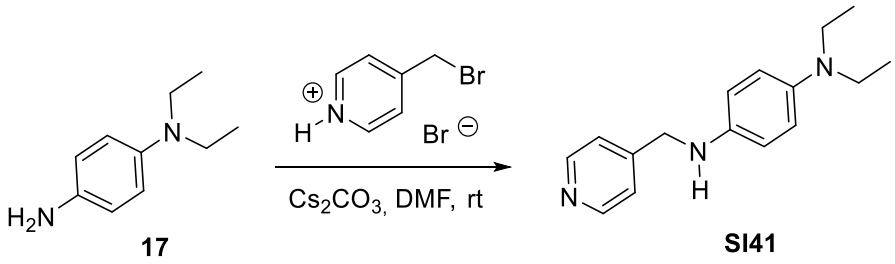
Synthesis according to the General procedure I. Deviating from the General procedure I, the reaction time was 2 d. 5-Methyl-3-phenyl-isoxazole-4-carboxylic acid **6** (25.0 mg, 0.123 mmol), 6-amino-2,2-dimethylchroman-4-one (23.5 mg, 0.123 mmol), HBTU (60.6 mg, 0.160 mmol, 1.3 equiv), DIPEA (42.8 µL, 0.246 mmol, 2 equiv), DMF (1.5 mL). Solvent for extraction: ether. Chromatography on silica gel gave compound **SI39** (41.0 mg, 0.109 mmol, 89%) as a slightly yellow solid. M.p. 167.0–168.4 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.41 (s, 1H), 8.07 (d, 1H, ^{3}J = 2.7 Hz), 7.74–7.65 (m, 3H), 7.53–7.45 (m, 3H), 6.99 (d, 1H, J = 8.9 Hz), 2.79 (s, 2H), 2.58 (s, 3H), 1.39 (s, 6H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 191.8, 169.8, 160.1, 159.7, 155.9, 131.7, 130.0, 128.8, 128.4, 128.0, 127.7, 119.4, 118.5, 116.3, 113.1, 79.3, 47.9, 25.9, 11.8 ppm. HRMS calc. for $C_{22}H_{21}N_2O_4$ $[M+H]^+$: 377.1501, found 377.1503.

6-[[(5-Methyl-3-phenylisoxazol-4-yl)methyl]amino]-2-phenyl-4*H*-chromen-4-one (SI40)



Synthesis according to the General procedure IX. Deviating from the General procedure IX, no sodium sulphate was used. Acetic acid (33.7 µL, 0.588 mmol), 5-methyl-3-phenylisoxazole-4-carbaldehyde (0.110 g, 0.588 mmol), 6-aminoflavone (139 mg, 0.588 mmol), THF (4 mL), a 1.0 M solution of sodium cyanoborohydride in THF (2.94 mL 2.94 mmol, 5 equiv, added 1 h later). Reaction time: 4 d; quenched with a saturated solution of $NaHCO_3$ in H_2O (5 mL) for 20 min. Solvents for extraction: ethyl acetate and a mixture of water and brine (3:1). Chromatography on silica gel gave compound **SI40** (30.6 mg, 0.0749 mmol, 13%) as a yellow solid. M.p. 185.0–186.4 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.10–8.03, 7.75–7.68 (each m, each 2H), 7.62–7.53 (m, 4H), 7.51–7.45 (m, 3H), 7.18 (dd, 1H, ^{3}J = 2.9 Hz, ^{3}J = 9.1 Hz), 7.05 (d, 1H, ^{3}J = 2.9 Hz), 6.92 (s, 1H), 6.34 (t, 1H, ^{3}J = 4.7 Hz), 4.14 (d, 2H, ^{3}J = 4.7 Hz), 2.50 (s, 3H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 177.0, 168.6, 162.0, 161.6, 148.4, 146.1, 131.5, 131.4, 129.7, 129.0, 128.9, 128.9, 127.8, 126.1, 124.1, 121.4, 119.1, 110.4, 105.9, 101.9, 36.2, 10.9 ppm. HRMS calc. for $C_{26}H_{21}N_2O_3$ $[M+H]^+$: 409.1552, found 409.1555.

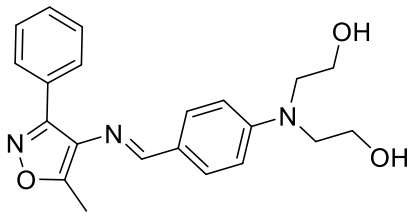
N^1,N^1-Diethyl-N^4-(pyridin-4-ylmethyl)benzene-1,4-diamine (SI41)



17 **SI41**

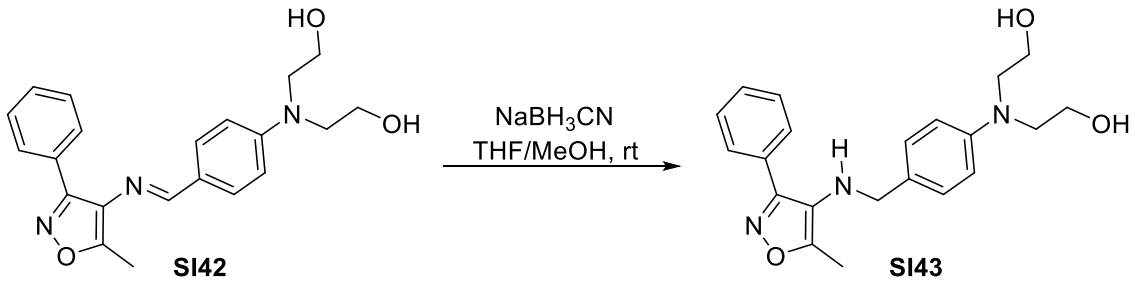
A mixture of *N*,*N*-diethyl-*p*-phenylenediamine **17** (98.6 µL, 0.593 mmol, 1.5 equiv), 4-(bromomethyl)pyridine hydrobromide (0.100 g, 0.395 mmol) and cesium carbonate (129 mg, 0.395 mmol) in absolute DMF (3 mL) was stirred for 3 d at room temperature under argon. The reaction mixture was diluted with ethyl acetate and washed three times with water. The solvent was removed with a rotary evaporator, and the crude product was subjected to automated preparative chromatography. The chromatography on silica gel was performed with an increasing gradient of ethyl acetate in *n*-hexane, starting with 0% of the ethyl acetate to give compound **SI41** (34.4 mg, 0.135 mmol, 34%) as a brown solid. M.p. 157.6–158.9 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.47 (m_c, 2H), 7.34 (m_c, 2H), 6.60–6.52 (bm, 2H), 6.50–6.43 (bm, 2H), 5.67 (t≈bs, 1H), 4.22 (bd, 2H, ^3J = 5.0 Hz), 3.10 (q, 4H, ^3J = 7.0 Hz), 0.96 (t, 6H, ^3J = 7.0 Hz) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 150.2, 149.3, 140.2, 139.9, 122.2, 116.3, 113.6, 46.4, 44.7, 12.3 ppm. HRMS calc. for $C_{16}H_{22}N_3$ $[M+H]^+$: 256.1814, found 256.1815.

(*E*)-2,2'-[[4-[[(5-Methyl-3-phenylisoxazol-4-yl)imino]methyl]phenyl]azanediyl]bis(ethan-1-ol) (SI42)



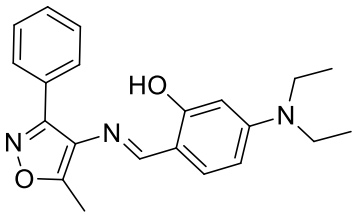
Synthesis according to the General procedure III. Deviating from the General procedure III, ethyl acetate was added to the reaction mixture to enhance solubility. Acetic acid was added after 8 h heating at 100 °C. After the addition of acetic acid, the reaction mixture was heated at 70 °C overnight. 4-[*N*,*N*-Bis(2-hydroxyethyl)amino]benzaldehyde (287 mg, 1.37 mmol), 5-methyl-3-phenylisoxazol-4-amine **28** (239 mg, 1.37 mmol), Na_2SO_4 (284 mg, 2.00 mmol), toluene (3 mL), ethyl acetate (1 mL). Chromatography on silica gel gave compound **SI42** (0.310 g, 0.848 mmol, 62%) as a yellowish solid. M.p. 153.0–154.2 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.37 (s, 1H), 7.95–7.87 (m, 2H), 7.68 (m_c, 2H), 7.53–7.43 (m, 3H), 6.80 (m_c, 2H), 4.78 (t, 2H, ^3J = 5.2 Hz, OH), 3.63–3.47 (m, 8H), 2.47 (s, 3H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 163.2, 156.6, 156.3, 150.9, 130.1, 129.5, 128.9, 128.6, 128.6, 127.5, 122.9, 111.1, 58.0, 53.1, 11.0 ppm. HRMS calc. for $C_{21}H_{24}N_3O_3$ $[M+H]^+$: 366.1818, found 366.1817.

2,2'-[[4-[[(5-Methyl-3-phenylisoxazol-4-yl)amino]methyl]phenyl]azanediyl]bis(ethan-1-ol) (SI43)



(*E*)-2,2'-[[4-[[(5-Methyl-3-phenylisoxazol-4-yl)imino]methyl]phenyl]azanediyl]diethanol **SI42** (0.200 g, 0.547 mmol) was dissolved under argon in a mixture of absolute THF (3.5 mL) and absolute MeOH (2 mL). Sodium cyanoborohydride (124 mg, 3.28 mmol, 6 equiv) was added and the reaction mixture was stirred for 2 d at room temperature. A saturated solution of sodium hydrogen carbonate in H_2O (8 mL) was added and the solution was stirred for 20 min at room temperature. EtOAc was added and the organic phase was washed three times water. The solvent was removed with a rotary evaporator, and the residue was subjected to automated preparative chromatography. The chromatography on silica gel was performed with an increasing gradient of MeOH in EtOAc, starting with 0% of MeOH. The solvents of the fractions still containing both the reaction product and starting material were removed with a rotary evaporator. Treating the residue with a small amount of MeOH led to crystallization of the starting material overnight (85.9 mg, 0.235 mmol). The solvent of the mother liquor was removed with a rotary evaporator and the residue was subjected to automated preparative chromatography. The chromatography on silica gel was performed with an increasing gradient of ethyl acetate in *n*-hexane, starting with 0% of ethyl acetate gave compound **SI43** (18.9 mg, 0.0514 mmol, 9%) as a yellow oil. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.92–7.84 (m, 2H), 7.55–7.44 (m, 3H), 7.93 (m_c, 2H), 6.56 (m_c, 2H), 4.68 (t, 2H, ^3J = 5.4 Hz), 4.27 (t, 1H, ^3J = 6.8 Hz), 3.69 (d, 1H), 3.55–3.46, 3.41–3.32 (each m, each 4H), 2.19 (s, 3H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 159.1, 157.4, 146.9, 129.4, 129.4, 128.9, 128.7, 127.1, 126.2, 123.2, 110.9, 58.1, 53.3, 51.4, 10.2 ppm. HRMS calc. for $C_{21}H_{26}N_3O_3$ $[M+Na]^+$: 390.1794, found 390.1797.

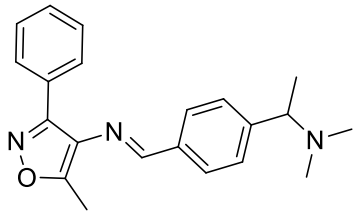
(*E*)-5-(Diethylamino)-2-[[(5-methyl-3-phenylisoxazol-4-yl)imino]methyl]phenol (SI44)



Synthesis according to the General procedure III. Deviating from the General procedure III, reaction mixture was heated at 70 °C overnight, 100 °C for 5 h before *p*-toluenesulfonic acid was added and then the reaction mixture was heated at 70 °C for 30 min. After cooling to rt, DIPEA (0.190 mL, 1.09 mmol) was added prior to the work-up procedure. 4-(Diethylamino)salicylaldehyde (211 mg, 1.09 mmol), 5-methyl-3-phenylisoxazol-4-amine **28** (0.190 g, 1.09 mmol), Na_2SO_4 (426 mg, 3.00 mmol), *p*-toluenesulfonic acid (51.9 mg, 0.273 mmol, 0.25 equiv), toluene (2.5 mL). Automated chromatography on silica gel gave compound **SI44** (304 mg, 0.870 mmol, 80%) as yellow crystals.

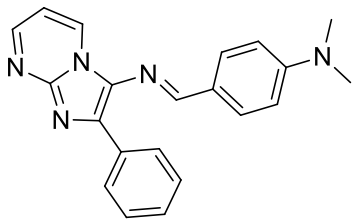
M.p. 120.9–121.8 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.61 (s, 1H), 8.54 (s, 1H), 7.77–7.70 (m, 2H), 7.55–7.48 (m, 3H), 7.29 (d, 1H, ^{3}J = 8.9 Hz), 6.32 (dd, 1H, ^{4}J = 2.4 Hz), 6.08 (d, 1H), 3.39 (q, 4H, ^{3}J = 7.0 Hz), 2.53 (s, 3H), 1.11 (t, 6H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 165.5, 162.2, 157.7, 157.0, 151.6, 133.8, 129.7, 128.8, 128.4, 127.5, 126.1, 108.3, 103.8, 96.8, 43.9, 12.4, 11.2 ppm. HRMS calc. for $C_{21}H_{24}N_3O_2$ $[M+H]^+$: 350.1869, found 350.1874.

(*E*)-*N*-[4-[1-(Dimethylamino)ethyl]benzylidene]-5-methyl-3-phenylisoxazol-4-amine (SI45)



Synthesis according to the General procedure III. Deviating from the General procedure III, the reaction mixture was first stirred at room temperature overnight and then heated at 70 °C for 2 h. 4-[1-(Dimethylamino)ethyl]benzaldehyde (50.0 mg, 0.282 mmol), 5-methyl-3-phenylisoxazol-4-amine **28** (49.1 mg, 0.282 mmol) Na_2SO_4 (80.1 mg, 0.564 mmol), AcOH (3.2 μL, 0.056 mmol, 0.2 equiv), toluene (2 mL). Chromatography on silica gel gave compound **SI45** (72.0 mg, 0.216 mmol, 77%) as a colorless oil. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.62 (s, 1H), 7.93–7.83 (m, 4H), 7.55–7.43 (m, 5H), 3.34 (q, 1H, ^{3}J = 6.7 Hz), 2.52 (s, 3H), 2.12 (s, 6H), 1.29 (d, 3H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 163.6, 157.2, 156.9, 148.4, 134.4, 129.7, 128.7, 128.5, 128.3, 127.7, 127.6, 64.5, 42.6, 19.6, 11.1 ppm. HRMS calc. for $C_{21}H_{24}N_3O$ $[M+H]^+$: 334.1919, found 334.1922.

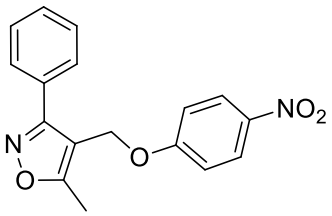
(*E*)-*N*-[4-(Dimethylamino)benzylidene]-2-phenylimidazo[1,2-*a*]pyrimidin-3-amine (SI46)



Synthesis according to the General procedure III. Deviating from the General procedure III, the reaction mixture was first stirred at room temperature for 3 d, heated at 65 °C overnight. Then *p*-toluenesulfonic acid was added, and the reaction mixture was heated at 70 °C for 4 h. 4-(Dimethylamino)benzaldehyde (49.5 mg, 0.332 mmol, 1.5 equiv), 2-phenylimidazo[1,2-*a*]pyrimidin-3-ylamine (46.4 mg, 0.221 mmol), Na_2SO_4 (62.8 mg, 0.442 mmol), AcOH (2.5 μL, 0.044 mmol, 0.2 equiv), *p*-toluenesulfonic acid (4.2 mg, 0.022 mmol, 0.1 equiv), toluene (1 mL). Automated chromatography on silica gel gave compound **SI46** (51.0 mg, 0.149 mmol, 68%) as yellow crystals. M.p. 199.1–200.4 °C (decomp.). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.86 (dd, 1H, ^{3}J = 6.9 Hz, ^{4}J = 2.0 Hz), 8.72 (s, 1H), 8.51 (dd, 1H, ^{3}J = 4.1 Hz), 7.97 (m_c, 2H), 7.77 (m_c, 2H), 7.44 (m_c, 2H), 7.33 (m_c, 1H), 7.05 (dd, 1H), 6.81 (m_c, 2H), 3.01 (s, 6H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.1, 152.9, 149.6, 144.5, 134.2, 132.8, 131.8, 130.4, 128.5, 128.1, 127.6, 123.3, 111.6, 108.9, 39.7 ppm. HRMS calc. for $C_{21}H_{20}N_5$ $[M+H]^+$: 342.1719, found 342.1723.

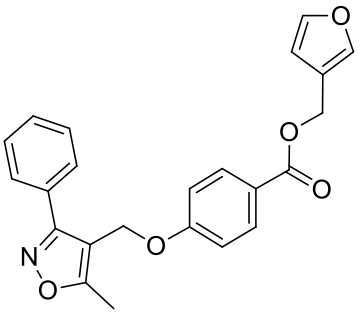
Preparation of compounds in Scheme 3 and other related compounds

5-Methyl-4-[(4-nitrophenoxy)methyl]-3-phenylisoxazole (34b)



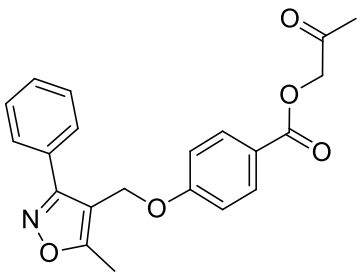
(5-Methyl-3-phenylisoxazol-4-yl)methanol **37** (189 mg, 1.00 mol), *p*-nitrophenol (167 mg, 1.20 mmol, 1.2 equiv) and triphenylphosphine (315 mg, 1.20 mmol, 1.2 equiv) were dissolved in anhydrous THF (4 mL) under argon and cooled to 0 °C in an ice bath. Diisopropyl azodicarboxylate (0.236 mL, 1.20 mmol, 1.2 equiv) was added, and the reaction mixture was stirred overnight, while the temperature was allowed to warm to rt. Diethyl ether was added, the organic phase was washed twice with water, twice with a 2 M solution of sodium hydroxide in water and several times with water until the aqueous phase remained neutral. The organic solvents were removed with a rotary evaporator, and the crude product was purified by automated chromatography on silica gel, using a gradient of increasing ethyl acetate starting with 100% *n*-hexane, followed by recrystallization (MeOH/ethyl acetate) to give compound **34b** (0.100 g, 0.322 mmol, 32%) as white crystals. M.p. 163.3–165.0 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.22 (m$_c$, 2H), 7.70–7.63 (m, 2H), 7.52–7.46 (m, 3H) 7.22 (m$_c$, 2H), 5.16 (s, 2H), 2.55 (s, 3H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 170.1, 163.1, 162.0, 141.2, 129.9, 129.0, 128.4, 127.7, 125.9, 115.4, 108.8, 59.9, 10.8 ppm. HRMS calc. for $C_{17}H_{15}N_2O_4$ [M+H]$^+$: 311.1032, found 311.1029.

Furan-3-ylmethyl 4-[(5-methyl-3-phenylisoxazol-4-yl)methoxy]benzoate (35c)



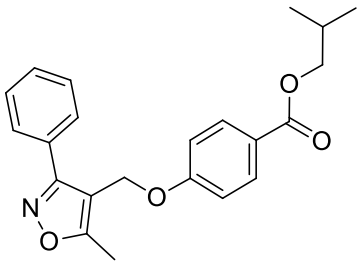
Synthesis according to the General procedure VII. 4-[(5-Methyl-3-phenylisoxazol-4-yl)methoxy]benzoic acid **38** (22.6 mg, 0.0731 mmol), 3-hydroxymethylfuran (18.8 μL, 0.219 mmol, 3 equiv), HBTU (41.6 mg, 0.110 mmol, 1.5 equiv), DIPEA (25.5 μL, 0.146 mmol, 2 equiv), DMF (1 mL). Reaction time: 2 d. Solvent for extraction: ethyl acetate. Chromatography on silica gel gave compound **35c** (16.7 mg, 0.0429 mmol, 59%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.02 (m$_c$, 2H), 7.70–7.63 (m, 2H), 5.55 (m$_c$, 1H), 7.48–7.38 (m, 3H), 6.96 (m$_c$, 2H), 6.50 (dd, 1H, ^{4}J = 0.9 Hz, ^{3}J = 1.9 Hz), 5.22 (s, 2H), 4.91 (s, 2H), 2.52 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.9, 166.1, 162.9, 162.1, 143.6, 141.7, 132.0, 130.0, 129.1, 129.0, 128.4, 123.6, 120.8, 114.6, 110.8, 109.3, 59.8, 58.3, 11.6 ppm. HRMS calc. for $C_{23}H_{20}NO_5$ [M+H]$^+$: 390.1341, found 390.1340.

2-Oxopropyl 4-[(5-methyl-3-phenylisoxazol-4-yl)methoxy]benzoate (35d)



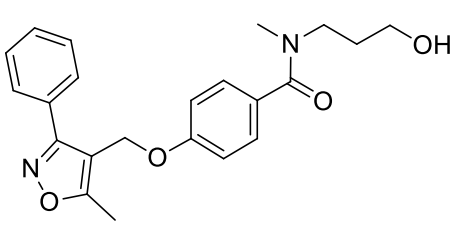
Synthesis according to the General procedure VII. 4-[(5-Methyl-3-phenylisoxazol-4-yl)methoxy]benzoic acid **38** (23.2 mg, 0.0750 mmol), hydroxyacetone (15.4 μL, 0.225 mmol, 3 equiv), HBTU (42.7 mg, 0.113 mmol, 1.5 equiv), DIPEA (26.1 μL, 0.150 mmol, 2 equiv), DMF (1 mL). Reaction time: 2 d. Solvent for extraction: diethyl ether. Chromatography on silica gel gave compound **35d** (18.9 mg, 0.0517 mmol, 69%) as an amorphous white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.07 (m_c, 2H), 7.71–7.63 (m, 2H), 7.48–7.38 (m, 3H), 6.98 (m_c, 2H), 4.92 (s, 2H), 4.85 (s, 2H), 2.52 (s, 3H), 2.23 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 202.0, 169.9, 165.5, 162.9, 162.4, 132.3, 130.0, 129.1, 129.0, 128.4, 122.6, 114.7, 109.2, 68.8, 59.9, 26.3, 11.6 ppm. HRMS calc. for $C_{21}H_{20}NO_5$ $[M+H]^+$: 366.1341, found 366.1342.

Isobutyl 4-[(5-methyl-3-phenylisoxazol-4-yl)methoxy]benzoate (35e)



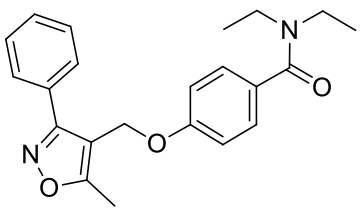
Synthesis according to the General procedure VII. 4-[(5-Methyl-3-phenylisoxazol-4-yl)methoxy]benzoic acid **38** (25.6 mg, 0.0828 mmol), isobutanol (22.9 μL, 0.248 mmol, 3 equiv), HBTU (47.1 mg, 0.124 mmol, 1.5 equiv), DIPEA (28.8 μL, 0.166 mmol, 2 equiv), DMF (1 mL). Reaction time: 2 d. Solvent for extraction: diethyl ether. Chromatography on silica gel gave compound **35e** (5.5 mg, 0.0151 mmol, 18%) as a colorless resin. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.03 (m_c, 2H), 7.71–7.64 (m, 2H), 7.48–7.39 (m, 3H), 6.97 (m_c, 2H), 4.91 (s, 2H), 4.10 (d, 2H, ^{3}J = 6.6 Hz), 2.52 (s, 3H), 2.08 (m_c, 1H), 1.03 (d, 3H, ^{3}J = 6.7 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.9, 166.3, 162.9, 162.0, 131.8, 130.0, 129.1, 129.0, 128.4, 124.1, 114.6, 109.3, 71.0, 59.8, 28.1, 19.4, 11.6 ppm. HRMS calc. for $C_{22}H_{24}NO_4$ $[M+H]^+$: 366.1705, found 366.1705.

***N*-(3-Hydroxypropyl)-*N*-methyl-4-[(5-methyl-3-phenylisoxazol-4-yl)methoxy]benzamide (36a)**



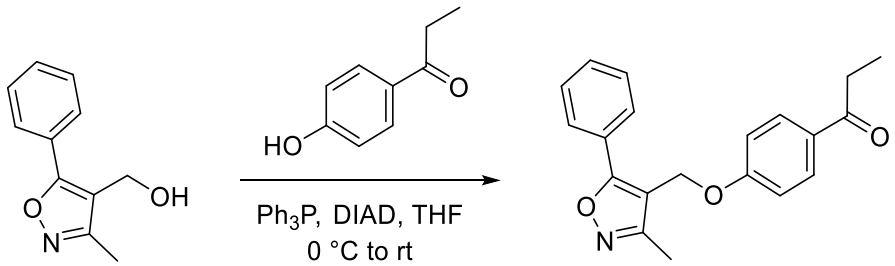
Synthesis according to the General procedure I. 4-[(5-Methyl-3-phenylisoxazol-4-yl)methoxy]benzoic acid **38** (21.3 mg, 0.0689 mmol), 3-(methylamino)propan-1-ol (20.1 mg, 0.207 mmol, 3 equiv), HBTU (33.9 mg, 0.0896 mmol, 1.5 equiv), DIPEA (24.0 μL, 0.138 mmol, 2 equiv), DMF (1 mL). Solvent for extraction: ethyl acetate. Chromatography on silica gel gave compound **36a** (20.3 mg, 0.0534 mmol, 77%) as a white solid. M.p. 63.6–68.3 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.73–7.66 (m, 2H), 7.53–7.46 (m, 3H), 7.35 (m_c, 2H), 7.03 (m_c, 2H), 5.02 (s, 2H), 4.41 (bs, 1H, OH), 3.51–3.31 (bm, 4H), 2.92 (s, 3H, N), 2.53 (s, 3H), 1.70 (bm_c, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.4, 162.5, 158.9, 130.4, 130.1, 129.4, 129.1, 128.3, 115.0, 109.8, 61.2, 59.6, 58.8, 31.1, 29.7, 11.3 ppm. HRMS calc. for $C_{22}H_{25}N_2O_4$ $[M+H]^+$: 381.1814, found 381.1814.

***N*,*N*-Diethyl-4-[(5-methyl-3-phenylisoxazol-4-yl)methoxy]benzamide (36b)**



Synthesis according to the General procedure I. 4-[(5-Methyl-3-phenylisoxazol-4-yl)methoxy]benzoic acid **38** (22.6 mg, 0.0731 mmol), diethylamine (22.7 mg, 0.219 mmol, 3 equiv), HBTU (36.0 mg, 0.0950 mmol, 1.3 equiv), DIPEA (25.5 μL, 0.146 mmol, 2 equiv), DMF (1 mL). Solvent for extraction: ethyl acetate and a mixture of water with 30% brine. Chromatography on silica gel gave compound **36b** (25.9 mg, 0.0711 mmol, 97%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.73–7.66 (m, 2H), 7.47–7.39 (m, 3H), 7.36 (m_c, 2H), 6.94 (m_c, 2H), 4.87 (s, 2H), 3.42 (bs, 4H), 2.50 (s, 3H), 1.19 (bt, 6H, ^{3}J = 7.1 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.1, 169.8, 162.9, 159.0, 130.7, 129.9, 129.1, 128.5, 128.0, 114.9, 109.5, 59.8, 44.0–38.5 (bs), 13.8, 11.5 ppm. HRMS calc. for $C_{22}H_{25}N_2O_3$ $[M+H]^+$: 365.1965, found 365.1870.

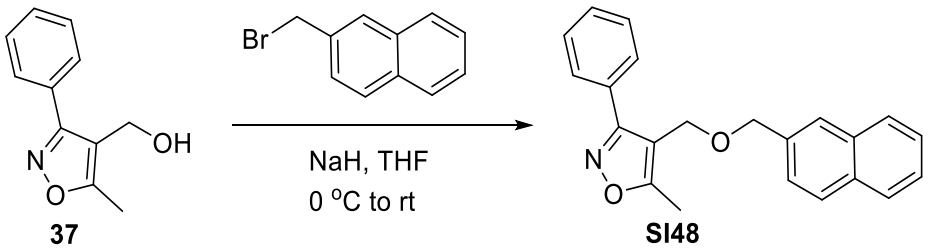
1-[4-[(3-Methyl-5-phenylisoxazol-4-yl)methoxy]phenyl]propan-1-one (SI47)



SI47

To a mixture of 3-methyl-5-phenylisoxazol-4-yl)methanol (0.100 g, 0.529 mmol), 4′-hydroxypropiophenone (95.2 mg, 0.634 mmol, 1.2 equiv) and triphenylphosphine (166 mg, 0.634 mmol, 1.2 equiv) in anhydrous THF (3 mL) and cooled to 0 °C in an ice bath, diisopropyl azodicarboxylate (0.125 mL, 0.634 mmol, 1.2 equiv) was added. The reaction mixture was stirred overnight under argon, while the temperature was allowed to warm to rt. Diethyl ether was added, the organic phase was washed three times with water and the organic solvent was removed with a rotary evaporator. The crude product was purified by automated chromatography on silica gel, using a gradient of increasing ethyl acetate starting with 100% *n*-hexane. Recrystallization ($MeOH/H_2O$ 10+1) gave compound **SI47** (93.7 mg, 0.292 mmol, 55%) as a white solid. M.p. 142.1–147.2 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.97 (m_c, 2H), 7.72–7.65 (m, 2H), 7.51–7.45 (m, 3H), 7.00 (m_c, 2H), 5.01 (s, 2H), 2.96 (q, 2H, ^{3}J = 7.3 Hz), 2.39 (s, 3H), 1.23 (t, 3H, ^{3}J = 7.3 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.5, 168.6, 162.0, 160.8, 131.0, 130.6, 130.5, 129.3, 127.6, 114.6, 109.5, 60.0, 31.7, 10.4, 8.6 ppm. HRMS calc. for $C_{20}H_{20}NO_3$ $[M+H]^+$: 322.1443, found 322.1443.

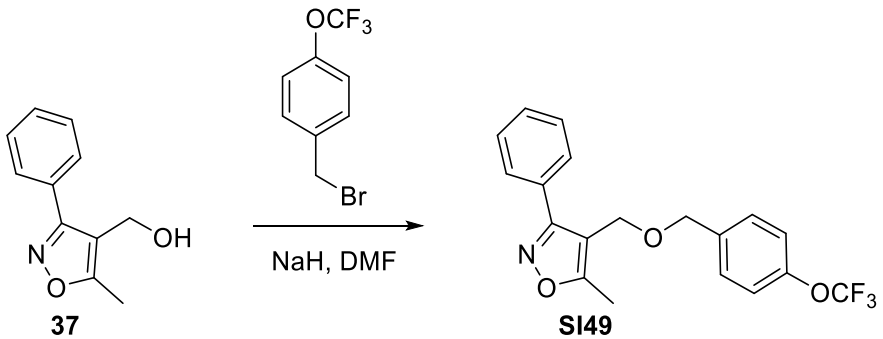
5-Methyl-4-[(naphthalen-2-ylmethoxy)methyl]-3-phenylisoxazole (SI48)



37 **SI48**

(5-Methyl-3-phenylisoxazol-4-yl)methanol **37** (94.6 mg, 0.500 mmol) was dissolved in anhydrous THF (3 mL) under argon, cooled to 0 °C in an ice bath, and a 60% dispersion of sodium hydride in mineral oil (40.0 mg, 1.00 mmol, 2 equiv) was added. After one hour, 2-(bromomethyl)naphthalene (94.9 μL, 0.593 mmol, 1.1 equiv) was added. The ice bath was removed, and the reaction mixture was stirred overnight at room temperature. Water and dichloromethane were added, the phases were separated and the organic phase was washed twice with water. The organic solvents were removed with a rotary evaporator, and the crude product was purified by automated chromatography on silica gel using a gradient starting with 100% *n*-hexane and ending with 100% diethyl ether to give compound **SI48** (121 mg, 0.367 mmol, 73%) as a colorless oil. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.95–7.73 (m, 6H), 7.56–7.43 (m, 6H), 4.70 (s, 2H), 4.45 (s. 2H), 2.48 (s, 3H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ169.5, 162.0, 135.5, 132.8, 132.5, 129.8, 128.9, 128.8, 127.9, 127.9, 127.7, 127.6, 126.3, 126.2, 126.0, 110.4, 70.2, 60.2, 10.9 ppm. HRMS calc. for $C_{22}H_{20}NO_2$ $[M+H]^+$: 330.1494, found 330.1494.

5-Methyl-3-phenyl-4-[[[4-(trifluoromethoxy)benzyl]oxy]methyl]isoxazole (SI49)



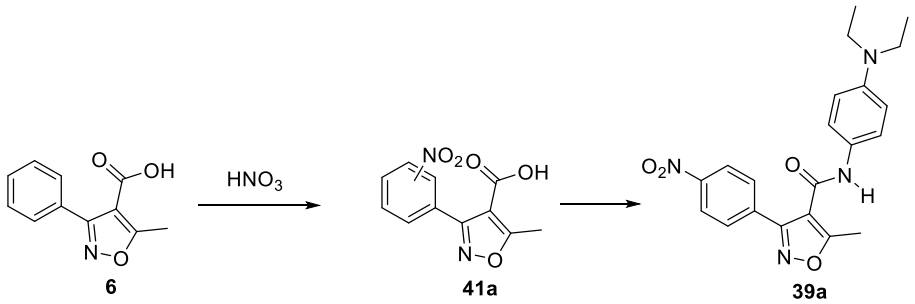
37 **SI49**

(5-Methyl-3-phenylisoxazol-4-yl)methanol **37** (102 mg, 0.539 mmol) was dissolved in anhydrous DMF (3 mL) under argon, cooled to 0 °C in an ice bath, and a 60% dispersion of sodium hydride in mineral oil (23.7 mg, 0.593 mmol, 1.1 equiv) was added. After one hour, 4-(trifluoromethyl)benzyl bromide (94.9 μL, 0.593 mmol, 1.1 equiv) was added. The ice bath was removed, and the reaction mixture was stirred overnight at room temperature. Potassium *tert*-butoxide (36.3 mg, 0.323 mmol, 0.6 equiv) was added and stirring was continued overnight. Diethyl ether was added, the organic

phase was washed three times with water, and the organic solvents were removed with a rotary evaporator. The crude product was purified by automated chromatography on silica gel to give compound **SI49** (67.0 mg, 0.184 mmol, 34%) as a colorless oil. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.76–7.69 (m, 2H), 7.53–7.47 (m, 3H,), 7.44 (m$_c$, 2H), 7.37–7.31 (m, 2H), 4.56 (s, 2H), 4.42 (s. 2H), 2.47 (s, 3H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 169.5, 162.0, 147.7, 137.5, 129.8, 129.6, 128.9, 128.8, 127.8, 121.0, 110.3, 70.2, 60.2, 10.8 ppm. HRMS calc. for $C_{19}H_{18}F_3NO_3$ [M+H]$^+$: 364.1161, found 364.1160.

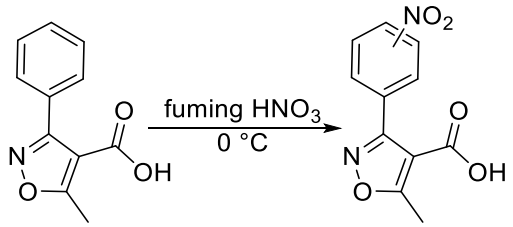
Preparation of compounds in Scheme 4 and other related compounds

N-[4-(Diethylamino)phenyl]-5-methyl-3-(4-nitrophenyl)isoxazole-4-carboxamide (39a)



Synthesis according to the General procedure I. Deviating from the General procedure I, the reaction mixture was diluted with ethyl acetate for the work-up and extracted once with a 2 M solution of sodium hydroxide in water and twice with 4 M hydrochloric acid. The combined hydrochloric acid phases were made alkaline with a 2 M solution of sodium hydroxide in water and extracted twice with ethyl acetate. The organic phase was washed twice with a mixture of water and brine (10:1). The starting material used for the synthesis of **39a** was the once recrystallized product mixture from the nitration of 5-methyl-3-phenylisoxazole-4-carboxylic acid (**41a:41g:41h**), consisting of different regioisomers with the 3-nitrophenyl derivative as a major component. **41a:41g:41h**, (248 mg, 1.00 mmol), *N*,*N*-diethyl-*p*-phenylenediamine hydrochloride **50** (236 mg, 1.18 mmol, 1.2 equiv), HBTU (759 mg, 2.00 mmol, 2 equiv), DIPEA (0.871 mL, 5.00 mmol, 5 equiv), DMF (5 mL). Recrystallization (twice from MeOH/H_2O 10+1) [without chromatography on silica gel] gave compound **39a** (62.0 mg, 0.157 mmol, 16%) as fine orange needles. M.p. 179.8–181.0 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.16 (s, 1H), 8.36 (m$_c$, 2H), 7.98 (m$_c$, 2H), 7.39 (m$_c$, 2H), 6.64 (m$_c$, 2H), 3.30 (q, 4H, ^3J = 7.0 Hz), 2.61 (s, 3H), 1.06 (t, 3H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 170.4, 158.9, 158.5, 148.3, 144.6, 134.4, 129.2, 127.0, 124.0, 121.1, 113.6, 111.7, 43.8, 12.4, 11.9 ppm. HRMS calc. for $C_{21}H_{22}N_4O_4$ [M+H]$^+$: 395.1719, found 395.1719.

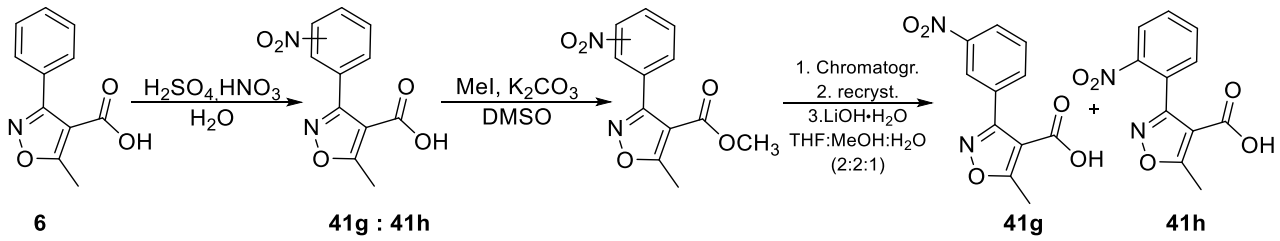
5-Methyl-3-(4-nitrophenyl)isoxazole-4-carboxylic acid (41a):(41g):(41h), crude



6 **41a:41g:41h**

5-Methyl-3-phenylisoxazole-4-carboxylic acid **6** (2.03 g, 10.0 mmol) was added in small portions to fuming nitric acid (12 mL), cooled to 0 °C in an ice bath. The reaction mixture was stirred at 0 °C for 1.5 h and quenched by addition of crushed ice. The precipitated product was obtained by filtration and after washing with water the wet solid was recrystallized from methanol to give compound **41a:41g:41h** (2.11 g, 8.49 mmol, 85%) as yellowish white crystals. The product is a mixture of the 3- (major), 4- and 2-nitrophenyl (minor) derivatives. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.32 (d, J = 9.0 Hz, 2H), 7.91 (d, J = 9.0 Hz, 2H), 2.73 (s, 3H).

5-Methyl-3-(3-nitrophenyl)isoxazole-4-carboxylic acid 41g and 5-methyl-3-(2-nitrophenyl)isoxazole-4-carboxylic acid (41h)



6 **41g : 41h** **41g** **41h**

Note: The reaction procedure has not been optimized. The compound **41g** can likely be obtained in much higher yield. **41h** is only a minor side product. The synthesis of **41g** is known (F. P. Doyle, J. C. Hanson, A. W. Long, J. H. C. Nayler, *J. Chem. Soc.* **1963**, 5845-5854) and **41h** is known (without experimental data): Z. Xin, H. Zhao, M. D. Sery, B. Liu, V. G. Schaefer, D. H. Falls, W. Kaszuska, C. A. Colins, H. L. Sham, G. Liu, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1201-1204.

5-Methyl-3-phenylisoxazole-4-carboxylic acid **6** (10.0 g, 49.2 mmol) was added in small portions during a period of 40 min to fuming nitric acid (60 mL), cooled to 0 °C in an ice bath. The reaction mixture was stirred at 0 °C for 4 h and quenched by addition of crushed ice (100 mL). Water (180 mL) was added slowly and the precipitated mixture of intermediates was obtained by filtration. The precipitate was washed with water and the wet solid was recrystallized from methanol to give an intermediate mixture of differently nitrated regioisomers (11.0 g, 44.2 mmol, 90%) as yellowish white crystals. This mixture of isomers was dissolved in DMSO (50 mL). Potassium carbonate (2.98 g, 53.0 mmol, 1.2 equiv) and iodomethane (5.50 mL, 88.4 mmol, 2 equiv) were added, and the reaction mixture was stirred for 5 d at room temperature. The reaction mixture was diluted with ethyl acetate

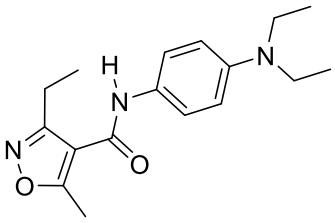
and washed three times with a mixture of water and brine (30%) and the organic solvent was removed with a rotary evaporator. The crude product was divided into five portions, which were separately purified by automated chromatography on silica gel, using a gradient of increasing acetone in *n*-hexane starting with 100% *n*-hexane. Hereby, the smaller second fraction was partially separated from the major first fraction. The combined second fractions were recrystallized from methanol/water (10+1) to give the intermediate methyl 5-methyl-3-(2-nitrophenyl)isoxazole-4-carboxylate (314 mg, 1.20 mmol, which was hydrolyzed by lithium hydroxide hydrate (64.8 mg, 1.54 mmol, 1.5 equiv) at room temperature overnight in a mixture of THF (1 mL), methanol (1 mL) and water (0.5 mL). This reaction mixture was diluted with water, washed once with diethyl ether, which in turn was re-extracted once with water. Ethyl acetate was added to the combined aqueous phases, which were acidified with 1 M hydrochloric acid. The phases were separated, and the organic phase was washed neutral with portions of water. The organic solvent was removed with a rotary evaporator, and the crude product was recrystallized from ethanol/water (10+1) to give compound **41h** (0.250 g, 1.01 mmol, 2%).

The combined major first fractions of the chromatography were recrystallized from *n*-hexane/benzene (2+1) and twice from ethanol/water (10 + 1) to give a mixture of the corresponding 3- and 4-nitro-substituted isoxazole methyl ester (3.48 g, 13.3 mmol) that contains methyl 5-methyl-3-(3-nitrophenyl)isoxazole-4-carboxylate as the major component. This mixture of intermediates was hydrolyzed by lithium hydroxide hydrate (835 mg, 19.9 mmol, 1.5 equiv) at room temperature overnight in a mixture of THF (12 mL), methanol (12 mL) and water (6 mL). This reaction mixture was diluted with water and washed once with diethyl ether. Diethyl ether was added, and the aqueous phase was acidified with 1 M hydrochloric acid. The phases were separated and the organic phase was washed neutral with portions of a mixture of water and brine (20%). The organic solvent was removed with a rotary evaporator, and the crude product was recrystallized twice from ethanol to give compound **41g** (741 mg, 2.99 mmol, 6%).

41h ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.25 (dd, $^{3,4}J$ = 8.1, 1.4 Hz, 1H), 7.89 (dd, $^{3,4}J$ = 7.5, 1.5 Hz, 1H), 7.84 (dd, $^{3,4}J$ = 5.1, 1.7 Hz, 1H), 7.80 (dd, $^{3,4}J$ = 7.6, 1.6 Hz, 1H), 7.66–7.51 (m, 1H), 2.72 (s, 3H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 174.9, 162.2, 160.7, 148.0, 133.9, 132.2, 131.3, 124.6, 124.0, 108.7, 12.8 ppm.

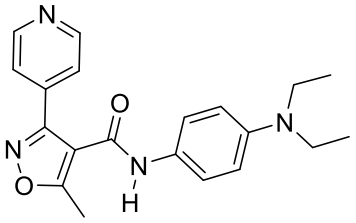
41g ^{1}H NMR (300 MHz, DMSO-d_6): δ 13.24 (br s, 1H), 8.48 (ddd, J = 2.3, 1.7, 0.5 Hz, 1H), 8.36 (ddd, J = 8.3, 2.4, 1.1 Hz, 1H), 8.10 (ddd, J = 7.7, 1.7, 1.1 Hz, 1H), 7.79 (ddd, J = 8.2, 7.7, 0.5 Hz, 1H), 2.73 (s, 3H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 176.1, 162.4, 160.5, 147.4, 135.7, 129.9, 129.7, 124.5, 124.0, 108.7, 13.1 ppm.

***N*-[4-(Diethylamino)phenyl]-3-ethyl-5-methylisoxazole-4-carboxamide (39b)**



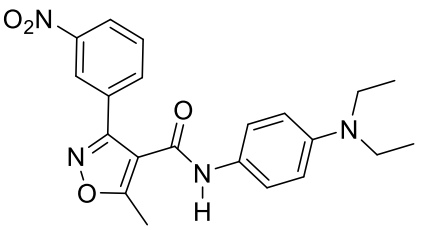
Synthesis according to the General procedure I. Deviating from the General procedure I, the reaction time was 4 d at room temperature. 3-Ethyl-5-methylisoxazole-4-carboxylic acid **41b** (0.100 g, 0.645 mmol), *N*,*N*-diethyl-*p*-phenylenediamine **17** (0.107 mL, 0.645 mmol), HBTU (318 mg, 0.839 mmol, 1.3 equiv), DIPEA (0.225 mL, 1.29 mmol, 2 equiv), DMF (3 mL). Solvent for extraction: diethyl ether. Chromatography on silica gel gave compound **39b** (127 mg, 0.421 mmol, 65%) as a greyish resin. M.p. 89.5–98.6 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.72 (s, 1H), 7.41 (m$_c$, 2H), 6.64 (m$_c$, 2H), 3.30 (q, 4H, ^{3}J = 7.0 Hz), 2.76 (q, 2H, ^{3}J = 7.5 Hz), 2.51 (s, 3H), 1.17 (t, 3H, ^{3}J = 7.5 Hz), 1.07 (t, 6H, ^{3}J = 7.0 Hz) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 168.6, 163.1, 159.3, 144.4, 127.3, 121.7, 113.2, 111.8, 43.7, 18.4, 12.3, 12.0, 11.9 ppm. HRMS calc. for $C_{17}H_{24}N_3O_2$ [M+H]$^+$: 302.1869, found 302.1870.

***N*-[4-(Diethylamino)phenyl]-5-methyl-3-(pyridin-4-yl)isoxazole-4-carboxamide (39c)**



Synthesis according to the General procedure I. 5-Methyl-3-(4-pyridinyl)-4-isoxazolecarboxylic acid **41c** (53.9 mg, 0.264 mmol), *N*,*N*-diethyl-*p*-phenylenediamine **17** (43.9 μL, 0.264 mmol), HBTU (0.130 g, 0.343 mmol, 1.3 equiv), DIPEA (92.0 μL, 0.604 mmol, 2 equiv), DMF (2 mL). Solvent for extraction: diethyl ether. Recrystallization (MeOH/H_2O 10+1) without chromatography on silica gel gave compound **39c** (43.0 mg, 0.123 mmol, 46%) as beige needles. M.p. 179.1–180.3 °C (decomp.). ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.13 (s, 1H), 8.72 (m$_c$, 2H), 7.68 (m$_c$, 2H), 7.40 (m$_c$, 2H), 6.64 (m$_c$, 2H), 3.30 (q, 4H, J = 7.0 Hz), 2.60 (s, 3H), 1.07 (t, 6H, J = 7.0 Hz) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 170.3, 158.4, 158.4, 150.3, 144.6, 135.6, 127.0, 122.0, 121.6, 113.6, 111.7, 43.7, 12.3, 11.9 ppm. HRMS calc. for $C_{20}H_{23}N_4O_2$ [M+H]$^+$: 351.1821, found 351.1822.

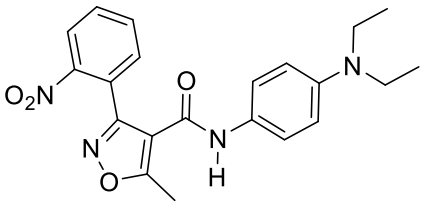
***N*-[4-(Diethylamino)phenyl]-5-methyl-3-(3-nitrophenyl)isoxazole-4-carboxamide (39g)**



Synthesis according to the General procedure I. 5-Methyl-3-(3-nitrophenyl)isoxazole-4-carboxylic acid **41g** (0.400 g, 1.61 mmol), *N*,*N*-diethyl-*p*-phenylenediamine **17** (0.268 mL, 1.61 mmol), HBTU (795 mg, 2.10 mmol, 1.3 equiv), DIPEA (0.562 mL, 3.22 mmol, 2 equiv), DMF (5 mL). Solvent for extraction: diethyl ether. Recrystallization (EtOH/H_2O 19+1) after chromatography on silica gel gave compound **39g** (538 mg, 1.36 mmol, 85%) as fine orange needles. M.p. 129.6–132.4 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.09 (s, 1H), 8.57 (dd≈t, 1H, ^{4}J = 2.0 Hz, ^{4}J = 2.0 Hz), 8.36 (ddd, 1H, ^{3}J = 8.3 Hz, ^{4}J = 1.0 Hz), 8.16 (ddd≈ddt, 1H, ^{3}J = 7.8 Hz), 7.82 (dd≈t, 1H), 7.38 (m$_c$, 2H), 6.64 (m$_c$, 2H), 3.30 (q, 4H, ^{3}J = 7.0 Hz), 2.62 (s, 3H), 1.07 (t, 6H, ^{3}J = 7.0 Hz) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 170.3, 158.6, 158.6, 147.9, 144.7, 134.1, 130.5, 129.7, 126.8,

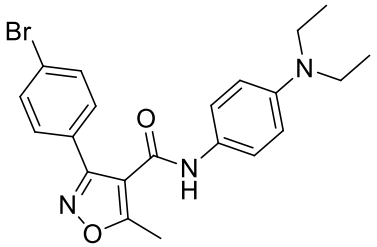
124.7, 122.3, 121.8, 113.4, 111.7, 43.7, 12.3, 11.9 ppm. HRMS calc. for $C_{21}H_{23}N_4O_4$ $[M+H]^+$: 395.1719, found 395.1722.

_N_-[4-(Diethylamino)phenyl]-5-methyl-3-(2-nitrophenyl)isoxazole-4-carboxamide (39h)



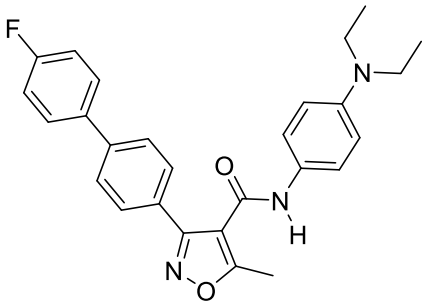
Synthesis according to the General procedure I. Deviating from the General procedure I the reaction time was 8 h at room temperature. 5-Methyl-3-(2-nitrophenyl)isoxazole-4-carboxylic acid **41h** (75.0 mg, 0.302 mmol), *N*,*N*-diethyl-*p*-phenylenediamine **17** (50.2 μL, 0.302 mmol), HBTU (149 mg, 0.393 mmol, 1.3 equiv), DIPEA (0.105 mL, 0.604 mmol, 2 equiv), DMF (1.5 mL). Solvent for extraction: diethyl ether. Recrystallization (MeOH/H_2O 10+1) after chromatography on silica gel gave compound **39h** (101 mg, 0.256 mmol, 85%) as yellow crystals. M.p. 136.6–137.8 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.71 (s, 1H), 8.17 (dd, 1H, ^3J = 8.0 Hz, ^4J = 1.4 Hz), 7.87 (ddd≈ddt, 1H, ^3J = 7.5 Hz, ^3J = 7.5 Hz), 7.79 (ddd≈ddt, 1H, ^4J = 1.6 Hz), 7.67 (dd, 1H), 7.27 (m_c, 2H), 6.59 (m_c, 2H), 3.28 (q, 4H, ^3J = 7.0 Hz), 2.68 (s, 3H), 1.05 (t, 6H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 168.9, 159.8, 158.2, 148.1, 144.5, 133.7, 132.1, 131.2, 126.8, 124.5, 123.3, 122.1, 113.5, 111.6, 43.7, 12.4, 12.3 ppm. HRMS calc. for $C_{21}H_{23}N_4O_4$ $[M+H]^+$: 395.1719, found 395.1722.

3-(4-Bromophenyl)-_N_-[4-(diethylamino)phenyl]-5-methylisoxazole-4-carboxamide (39i)



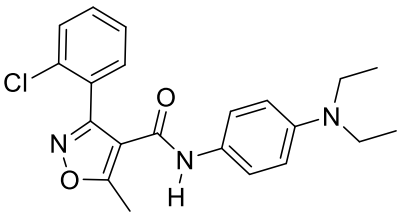
Synthesis according to the General procedure I. 3-(4-Bromophenyl)-5-methylisoxazole-4-carboxylic acid **41i** (503 mg, 1.78 mmol), *N*,*N*-diethyl-*p*-phenylenediamine **17** (0.296 mL, 1.78 mmol), HBTU (879 mg, 2.32 mmol, 1.3 equiv), DIPEA (0.621 mL, 3.56 mmol, 2 equiv), DMF (10 mL). Solvent for extraction: ethyl acetate. Recrystallization (EtOH/H_2O 10+1) after chromatography on silica gel gave compound **39i** (501 mg, 1.17 mmol, 66%) as light blue crystals. M.p. 157.8–159.3 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.08 (s, 1H), 7.96 (m_c, 4H), 7.40 (m_c, 2H), 6.64 (m_c, 2H), 3.30 (q, 4H, ^3J = 7.0 Hz), 2.57 (s, 3H), 1.07 (t, 6H, ^3J = 7.0 Hz) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 169.7, 159.3, 158.8, 144.5, 131.8, 129.7, 127.4, 127.1, 123.6, 121.6, 113.6, 111.7, 43.7, 12.3, 11.8 ppm. HRMS calc. for $C_{21}H_{23}BrN_3O_2$ $[M+H]^+$: 428.0974, found 428.0974.

_N_-[4-(Diethylamino)phenyl]-3-[4'-fluoro-[1,1'-biphenyl]-4-yl]-5-methylisoxazole-4-carboxamide (39j)



3-(4-Bromophenyl)-*N*-[4-(diethylamino)phenyl]-5-methylisoxazole-4-carboxamide **39i** (0.075 g, 0.175 mmol) was dissolved under argon in absolute toluene (2 mL). (4-Fluorophenyl)boronic acid (27.0 mg, 0.193 mmol, 1.1 equiv), ethanol (1 mL) and a 2.0 M solution of sodium carbonate in H_2O (1 mL) were added, and the mixture was degassed. Tetrakis(triphenylphosphine)palladium(0) (10.1 mg, 0.00875 mmol, 5 mol%) was added under argon, and the reaction mixture was heated at 80 °C under reflux conditions for 5 h and and to 70 °C overnight. Ethyl acetate was added, and the organic phase was washed three times with a mixture of water and brine (3:1). The solvent was removed with a rotary evaporator, and the crude product was subjected to automated preparative chromatography. The chromatography on silica gel was performed with an increasing gradient of ethyl acetate in *n*-hexane, starting with 0% of ethyl acetate gave compound **39j** (53.1 mg, 0.120 mmol, 68%) as a white solid. M.p. 171.2–173.9 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74 (m_c, 4H), 7.65–7.57 (m, 2H), 7.21–7.08 (m, 4H), 6.97 (bs, 1H), 6.58 (m_c, 2H), 3.30 (q, 4H, ^3J = 7.0 Hz), 2.78 (s, 3H), 1.12 (t, 6H, ^3J = 7.0 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.5, 164.7, 161.4, 159.7, 159.4, 145.7, 142.6, 136.2 (d, J = 3.6 Hz), 129.8, 129.0 (d, J = 8.1 Hz), 127.9, 127.1, 125.8, 122.3, 116.1 (d, J = 21.8 Hz), 112.3, 111.8, 44.7, 13.2, 12.6 ppm. HRMS calc. for $C_{27}H_{27}FN_3O_2$ $[M+H]^+$: 444.2087, found 444.2094.

3-(2-Chlorophenyl)-*N*-[4-(diethylamino)phenyl]-5-methylisoxazole-4-carboxamide (39k)



Synthesis according to the General procedure I. 3-(2-Chlorophenyl)-5-methylisoxazole-4-carboxylic acid **41k** (75.0 mg, 0.316 mmol), *N*,*N*-diethyl-*p*-phenylenediamine **17** (52.5 μL, 0.316 mmol), HBTU (156 mg, 0.411 mmol, 1.3 equiv), DIPEA (0.110 mL, 0.632 mmol, 2 equiv), DMF (1.5 mL). Solvent for extraction: diethyl ether. Recrystallization (MeOH/H_2O 10+1) after chromatography on silica gel gave compound **39k** (90.0 mg, 0.234 mmol, 74%) as fine white needles. M.p. 111.5–113.9 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.66 (s, 1H), 7.60–7.43 (m, 4H), 7.29 (m_c, 2H), 6.60 (m_c, 2H), 3.28 (q, 4H, ^3J = 7.0 Hz), 2.65 (s, 3H), 1.05 (t, 6H, ^3J = 7.0 Hz) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 169.1, 159.8, 158.5, 144.4, 132.4, 131.7, 131.4, 129.5, 127.6, 127.2, 127.2, 121.7, 114.8, 111.7, 43.7, 12.3, 12.1 ppm. HRMS calc. for $C_{21}H_{23}ClN_3O_2$ $[M+H]^+$: 384.1479, found 384.1475.

3-(4-Bromothiophen-2-yl)-*N*-[4-(diethylamino)phenyl]-5-methylisoxazole-4-carboxamide (39l)

i. (E/Z)-5-Bromothiophene-3-carbaldehyde oxime (**43l**)

To a solution of 5-bromothiophene-3-carbaldehyde (1.00 g, 5.23 mmol) in EtOH (12 mL) hydroxylamine hydrochloride (0.400 g, 5.76 mmol, 1.1 equiv) and pyridine (0.466 mL, 5.75 mmol, 1.1 equiv) were added. After stirring at room temperature for 2.5 h, the reaction mixture was quenched with a mixture of a saturated aqueous solution of NH_4Cl (10 mL) and water (5 mL). The aqueous phase was extracted with ethyl acetate (3 × 50 mL). The combined organic phases were dried with Na_2SO_4, and the solvents were evaporated *in vacuo* to yield after recrystallization (EtOH/water 10+1) compound **43k** (0.310 g, 1.50 mmol, 29%), which was used without further purification in the next step.

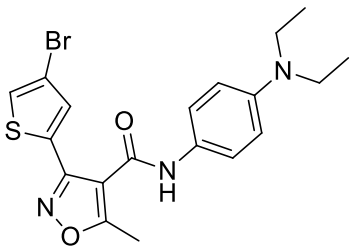
ii. 3-(4-Bromothiophen-2-yl)-5-methylisoxazole-4-carboxylate (**45l**)

Diacetoxyiodobenzene (354 mg, 1.10 mmol, 1.1 equiv) was dissolved in a mixture of MeOH (4 mL) and water (400 µL) and stirred at 0 °C in an ice bath. Trifluoroacetic acid (15 µL) and (*E*/*Z*)-4-bromothiophene-2-carbaldehyde oxime **43l** (206 mg, 1.00 mmol) were added, and after 2 min ethyl but-2-ynoate (82.8 µL, 1.10 mmol, 1.1 equiv) was added. The reaction mixture was stirred for 30 min at 0 °C, after which the ice-bath was removed and stirring was continued at room temperature for 1.5 h. The solvent was removed with a rotary evaporator, and the crude product mixture was subjected to automated preparative chromatography. The chromatography on silica gel was performed with an increasing gradient of ethyl acetate in *n*-hexane, starting with 0% of ethyl acetate. The chromatography gave 81.1 mg of a product mixture containing ethyl 3-(4-bromothiophen-2-yl)-5-methylisoxazole-4-carboxylate **45l**, which was used without further purification in the next step.

iii. 3-(4-Bromothiophen-2-yl)-5-methylisoxazole-4-carboxylic acid (**41l**)

3-(4-Bromothiophen-2-yl)-5-methylisoxazole-4-carboxylate **45l** was dissolved in an equimixture of THF, MeOH and water (1.5 mL). Lithium hydroxide hydrate (16.1 mg, 0.385 mmol) was added and the reaction mixture was stirred overnight at room temperature. Ethyl acetate was added, and the organic phase was extracted twice with water. The combined aqueous phases were washed once with diethyl ether, acidified with a 1 M solution of HCl in H_2O and extracted with ethyl acetate. The organic phase was washed twice with water and once with a mixture of water and brine (2:1) until the aqueous phase remained neutral. Evaporation of the organic phase with a rotary evaporator and drying in an oil pump vacuum gave crude 3-(4-bromothiophen-2-yl)-5-methylisoxazole-4-carboxylic acid **41l** (19.3 mg), which was used without purification.

iv. 3-(4-Bromothiophen-2-yl)-N-[4-(diethylamino)phenyl]-5-methylisoxazole-4-carboxamide (**39l**)



Synthesis according to the General procedure I. Deviating from the General procedure I, HATU was used as a coupling reagent. 3-(4-Bromothiophen-2-yl)-5-methylisoxazole-4-carboxylic acid **41l** (19.3 mg, crude), *N*,*N*-diethyl-*p*-phenylenediamine **17** (12.2 µL, 0.0737 mmol), HATU (33.1 mg, 0.0871 mmol) and DIPEA (23.3 µL, 0.134 mmol), DMF (0.5 mL). Solvent for extraction: diethyl ether. Chromatography on silica gel gave compound **39l** (18.5 mg, 0.0426

mmol, 4%) as a yellow solid. M.p. 125.1–128.3 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.18 (s, 1H), 7.89 (d, 1H, ^{3}J = 1.5 Hz), 7.61 (d, 1H, ^{3}J = 1.5 Hz), 7.44 (m$_c$, 2H), 6.67 (m$_c$, 2H), 3.32 (q, 4H, ^{3}J = 7.0 Hz), 2.57 (s, 3H), 1.08 (t, 6H, ^{3}J = 7.0 Hz) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 170.1, 158.3, 154.0, 144.7, 130.9, 130.5, 126.8, 126.5, 121.7, 112.7, 111.7, 109.2, 43.7, 12.3, 12.0 ppm. HRMS calc. for $C_{19}H_{21}BrN_3O_2S$ $[M+H]^+$: 434.0538, found 434.0540.

_N_-[4-(Diethylamino)phenyl]-5-methyl-3-(thiophen-3-yl)isoxazole-4-carboxamide (39m)

i. (E/Z)-thiophenecarbaldehyde oxime (**43m**)

To a solution of thiophene-3-carbaldehyde, **44m** (0.493 g, 4.40 mmol) in EtOH (9 mL), hydroxylamine hydrochloride (0.336 g, 4.84 mmol, 1.1 equiv) and pyridine (0.391 mL, 4.84 mmol, 1.1 equiv) were added. After stirring at room temperature for 2 h, the reaction mixture was quenched with a mixture of a saturated solution of NH_4Cl in H_2O (10 mL) and water (5 mL). The aqueous phase was extracted with ethyl acetate (3 × 20 mL). The combined organic phases were dried with anhydrous Na_2SO_4, and the solvents were evaporated *in vacuo* to yield compound **43m** (504 mg, 3.96 mmol, 90%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.55 (br s, 1H), 8.19 (s, 1H, major), 8.17 (dd, $^{3,4}J$ = 3.0, 1.2 Hz, 1H, minor), 7.51 (d, $^{3,4}J$ = 5.1, 1.2 Hz, minor), 7.48 (dd, $^{3,4}J$ = 3.0 Hz, 1.2 Hz, 1H, major), 7.41 (d, ^{4}J = 1.2 Hz, 1H, minor), 7.39 (d, 1H, ^{4}J = 1.2 Hz, major), 7.34–7.31 (m, 1H, minor), 7.34 (d, ^{3}J = 2.9 Hz, 1H, major) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.0, 145.7, 141.4, 134.5, 131.5, 129.6, 126.9, 126.7, 125.3, 124.9 ppm.

ii. Ethyl 5-methyl-3-(thiophen-3-yl)isoxazole-4-carboxylate (**45m**)

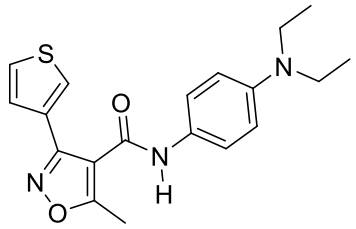
A solution of (*E/Z*)-thiophenecarbaldehyde oxime **43m** (0.137 g, 1.08 mmol) in MeOH (6 mL) was added dropwise to a stirred solution of ethyl 2-butynoate (0.138 mL, 1.19 mmol 1.1 equiv) and (diacetoxyiodo)benzene (382 mg, 1.19 mmol, 1.1 equiv) in MeOH (10 mL) at 0 °C followed by three drops of trifluoroacetic acid. The solution was stirred for 1 h at 0 °C, allowed to warm to rt and stirred at room temperature for further 2 h. The solvents were evaporated *in vacuo*, and the crude product mixture (383 mg) was subjected to a purification by an automated flash silica chromatography (*n*-hexane/EtOAc, 5:1), which yielded compound **45m** (81.0 mg, 0.341 mmol, 32%) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.06 (dd, $^{3,4}J$ = 3.0, 1.2 Hz, 1H), 7.53 (dd, $^{3,4}J$ = 5.1, 1.3 Hz, 1H), 7.36 (dd, $^{3,4}J$ = 5.1, 3.0 Hz, 1H), 4.32 (q, ^{3}J = 7.1 Hz, 2H), 2.71 (s, 3H), 1.34 (t, ^{3}J = 7.1 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.9, 162.2, 157.9, 128.3, 127.9, 125.3, 108.4, 61.0, 14.3, 13.9 ppm. This crude product was used in the next step without further purification.

iii. 5-Methyl-3-(thiophen-3-yl)isoxazole-4-carboxylic acid (**41m**)

Ethyl 5-methyl-3-(thiophen-3-yl)isoxazole-4-carboxylate **45m** (64.0 mg, 0.270 mmol) was dissolved in an equimixture of MeOH/H_2O (8 mL), and NaOH (21.5 mg, 0.539 mmol, 2 equiv) was added. The reaction mixture was stirred at 60 °C for 22 h, and then most of the MeOH was removed by evaporation *in vacuo*. The aqueous layer was acidified with a 1 M solution of HCl in H_2O to pH 1, and extracted with ethyl acetate (3 × 20 mL). The combined organic phases were washed with brine (20 mL), and the solvents were evaporated *in vacuo* to give compound **41m** (45.0 mg, 0.215 mmol, 80%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.09 (dd, $^{3,4}J$ = 3.0, 1.2 Hz, 1H), 7.56 (dd, $^{3,4}J$ = 5.1, 1.3 Hz,

1H), 7.37 (dd, $^{3,4}J$ = 5.1, 2.9 Hz, 1H), 2.77 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.0, 167.4, 157.9, 128.4, 128.3, 128.1, 125.5, 107.5, 14.2 ppm.

iv. N-[4-(Diethylamino)phenyl]-5-methyl-3-(thiophen-3-yl)isoxazole-4-carboxamide (**39m**)



5-Methyl-3-(thiophen-3-yl)isoxazole-4-carboxylic acid **41m** (18.0 mg, 0.0861 mmol) was dissolved in dry DMF (2 mL) under argon, and *N*,*N*-diethyl-*p*-phenylenediamine **17** (14.3 µL, 0.0861 mmol), HBTU (42.4 mg, 0.112 mmol, 1.3 equiv), and DIPEA (30.0 µL, 0.172 mmol, 2 equiv) were added to the solution. The reaction mixture was stirred for 16 h at room temperature. Diethyl ether (20 mL) was added, and the organic phase was washed with water (2 × 10 mL). The solvent was removed *in vacuo*, and the crude product mixture was subjected to a purification by an automated flash silica chromatography (*n*-hexane/EtOAc 1:0→0:1) to yield compound **39m** (17 mg, 55%). M.p. 137.0 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.82 (dd, $^{3,4}J$ = 3.0, 1.3 Hz, 1H), 7.52 (dd, $^{3,4}J$ = 5.0, 3.0 Hz, 1H), 7.44 (dd, $^{3,4}J$ = 5.0, 1.3 Hz, 1H), 7.20 (m_c, 2H), 6.62 (m_c, 2H), 3.32 (q, ^3J = 7.0 Hz, 4H), 2.73 (s, 3H), 1.14 (t, ^3J = 7.0 Hz, 6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.7, 159.1, 155.6, 145.5, 128.4, 127.6, 127.4, 127.3, 125.7, 121.9, 112.2, 111.7, 44.5, 12.9, 12.5 ppm. HRMS calc. for $C_{19}H_{21}N_3O_2S$ $[M+H]^+$: 356.1433, found 356.1439.

_N_-[4-(Diethylamino)phenyl]-3-(furan-3-yl)-5-methylisoxazole-4-carboxamide (39n)

i. (E/Z)-Furan-3-carbaldehyde oxime (**43n**)

To a solution of furan-3-carbaldehyde **44n** (423 mg, 4.40 mmol) in EtOH (9 mL), hydroxylamine hydrochloride (0.336 g, 4.84 mmol, 1.1 equiv) and pyridine (0.391 mL, 4.84 mmol, 1.1 equiv) were added. After stirring at room temperature for 1 h, the reaction mixture was quenched with a mixture of a saturated solution of NH_4Cl in H_2O (10 mL) and water (5 mL). The aqueous phase was extracted with ethyl acetate (3 × 20 mL). The combined organic phases were dried with Na_2SO_4, and the solvents were evaporated *in vacuo* to yield compound **43n** (327 mg, 2.94 mmol, 67%) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.36 (br, s, 1H), 8.29–8.16 (m, 1H, major), 8.08 (s, 1H, minor), 7.64 (t, J = 1.1 Hz, 1H, minor), 7.44 (t, J = 1.7 Hz, 1H, major), 7.42 (t, J = 1.7 Hz, 1H, minor), 7.35 (s, 1H, major), 6.71–6.68 (m, 1H, minor), 6.67 (dd, J = 1.9, 0.7 Hz, 1H, major). ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.1 (pyridine), 147.2 (major), 144.3 (minor), 143.6 (minor), 142.8 (major), 142.5 (minor), 139.8 (major), 137.2 (pyridine), 124.2 (pyridine), 119.9 (C, minor), 116.3 (C, major), 110.9 (CH, major), 107.4 (CH, minor) ppm.

ii. Ethyl 3-(furan-3-yl)-5-methylisoxazole-4-carboxylate (**45n**)

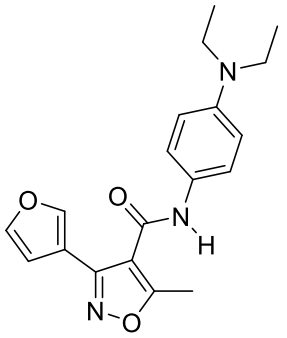
A solution of (*E/Z*)-furan-3-carbaldehyde oxime **43n** (111 mg, 1.00 mmol) in MeOH (6 mL) was added dropwise to a stirred solution of ethyl 2-butynoate (0.128 mL, 1.10 mmol 1.1 equiv) and (diacetoxyiodo)benzene (354 mg, 1.10 mmol, 1.1 equiv) in MeOH (10 mL) at 0 °C, followed by three drops of trifluoroacetic acid. The resulting solution was stirred for 1 h at 0 °C and allowed to warm to rt and stirred at room temperature for further 2 h. The solvents were evaporated *in vacuo*, and the crude product mixture (260 mg) was subjected to a purification by an automated flash silica

chromatography (*n*-hexane/EtOAc 20:1), which yielded compound **45n** (41.0 mg, 0.185 mmol, 19%). The product was used in the next step without further purification.

iii. 3-(Furan-3-yl)-5-methylisoxazole-4-carboxylic acid (**41n**)

To a solution of ethyl 5-methyl-3-(thiophen-3-yl)isoxazole-4-carboxylate **45n** (27 mg, 0.12 mmol) in an equimixture of MeOH/H_2O (3.5 mL), NaOH (21 mg, 0.54 mmol, 2.0 equiv) was added. The reaction mixture was stirred at 60 °C for 22 h and then most of the MeOH was removed *in vacuo*. The aqueous layer was acidified with a 1 M solution of HCl in H_2O to pH 1, and extracted with ethyl acetate (3 × 20 mL). The combined organic phases were washed with brine (20 mL), and the solvents were evaporated *in vacuo* to give compound **41n** (19.0 mg, 0.0983 mmol, 81%). The product was used in the next step without further purification.

iv. N-[4-(Diethylamino)phenyl]-3-(furan-3-yl)-5-methylisoxazole-4-carboxamide (**39n**)



To a solution of 3-(furan-3-yl)-5-methylisoxazole-4-carboxylic acid **41n** (19.0 mg, 0.091 mmol) in dry DMF (2 mL), *N*,*N*-diethyl-*p*-phenylenediamine **17** (16.4 µL, 0.100 mmol, 2.0 equiv), HBTU (44.8 mg, 0.118 mmol, 1.3 equiv), and DIPEA (32 µL, 0.182 mmol, 2.0 equiv) were added under argon. The reaction mixture was stirred for 16 h at room temperature. Diethyl ether (20 mL) was added, and the organic phase was washed with water (2 × 10 mL). The solvent was removed *in vacuo*, and the crude product mixture was subjected to a purification by an automated flash silica chromatography (*n*-hexane/EtOAc 1:0→1:1) to yield compound **39m** (18.0 mg, 0.0530 mmol, 59%). M.p. 136.6 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.04 (s, 1H), 8.15 (dd, $^{3,4}J$ = 1.5, 0.8 Hz, 1H), 7.81 (m$_c$, 1H), 7.44 (m$_c$, J = 9.0 Hz, 2H), 6.85 (dd, $^{3,4}J$ = 1.9, 0.8 Hz, 1H), 6.66 (m$_c$, 2H), 3.31 (q, ^3J = 7.0 Hz, 4H), 2.56 (s, 3H), 1.07 (t, ^3J = 7.0 Hz, 6H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 169.1, 158.9, 153.5, 144.6, 144.2, 142.8, 127.1, 121.7, 114.0, 113.0, 111.8, 109.0, 43.7, 12.3, 11.9 ppm. HRMS calcd. for $C_{19}H_{21}N_3O_3$ $[M+H]^+$: 340.1661, found 340.1664.

_N_-[4-(Diethylamino)phenyl]-5,5'-dimethyl-[3,3'-biisoxazole]-4-carboxamide (39o)

i. (E/Z)-5-Methylisoxazole-3-carbaldehyde oxime (**43o**)

To a solution of 5-methylisoxazole-3-carbaldehyde **44o** (0.200 g, 1.80 mmol) in MeOH (8 mL), hydroxylamine hydrochloride (138 mg, 1.98 mmol, 1.1 equiv) and sodium acetate (0.207 g, 2.52 mmol, 1.4 equiv) were added. After stirring at room temperature for 1 h, the reaction mixture was quenched with a mixture of a saturated solution of NH_4Cl in H_2O (10 mL) and water (5 mL). The aqueous phase was extracted with dichloromethane (3 × 20 mL). The combined organic phases were dried with anhydrous Na_2SO_4, and the solvents were evaporated *in vacuo* to yield crude compound **43o** (225 mg) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.16 (s, 1H, minor), 11.94 (s, 1H, major), 8.13 (s, 1H, major), 7.61 (s, 1H, minor), 6.80 (d, J = 1.0 Hz, 1H, minor), 6.44 (d, J = 0.7 Hz,

1H, major), 2.45 (d, J = 0.9 Hz, 3H, minor), 2.43 (d, J = 0.9 Hz, 3H, major). ^{13}C NMR (75 MHz, DMSO-d_6) δ 169.9, 158.5, 154.5, 139.2, 135.5, 103.9, 98.7, 14.1, 11.7 ppm.

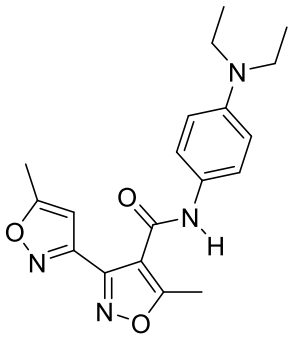
ii. Ethyl 5,5'-dimethyl-[3,3'-biisoxazole]-4-carboxylate (**45o**)

To a stirred solution of (*E/Z*)-5-methylisoxazole-3-carbaldehyde oxime **43o** (126 mg, 1.00 mmol), ethyl 2-butynoate (0.140 mL, 1.20 mmol, 1.2 equiv) and PhI (40.8 mg, 0.200 mmol, 0.20 equiv) in H_2O (6 mL) was added Oxone® (922 mg, 3.00 mmol, 3.0 equiv) in small portions. The resulting solution was stirred at room temperature for 18 h, and the aqueous phase was extracted with dichloromethane (3 × 4 mL). The combined organic phases were dried with anhydrous Na_2SO_4, and the solvents were evaporated *in vacuo*. The crude product mixture was subjected to a purification by an automated flash silica chromatography (*n*-hexane/EtOAc, 10:1) to yield compound **45o** (17 mg, 7.0%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.40 (q, J = 0.9 Hz, 1H), 4.30 (q, J = 7.1 Hz, 2H), 2.73 (s, 3H), 2.50 (d, J = 0.9 Hz, 3H), 1.30 (t, J = 7.1 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.9, 169.8, 161.3, 153.6, 153.5, 109.3, 103.0, 61.2, 14.2, 13.4, 12.3 ppm.

iii. 5,5'-Dimethyl-[3,3'-biisoxazole]-4-carboxylic acid (**41o**)

To a solution of ethyl 5,5'-dimethyl-[3,3'-biisoxazole]-4-carboxylate **45o** (16.8 mg, 0.075 mmol) in an equimixture of MeOH/H_2O (2.2 mL), NaOH (6.0 mg, 0.15 mmol, 2.0 equiv) was added. The reaction mixture was stirred at room temperature for 28 h and then most of the MeOH was removed *in vacuo*. The aqueous layer was acidified with a 1 M solution of HCl in H_2O to pH 1, and then extracted with dichloromethane (3 × 10 mL). The organic phase was dried with Na_2SO_4 and the solvents were evaporated *in vacuo* to give compound **41o** (14.2 mg, 91%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.67 (d, J = 0.9 Hz, 1H), 2.85 (s, 4H), 2.58 (d, J = 0.9 Hz, 4H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 180.4, 171.7, 160.7, 154.4, 149.8, 108.4, 101.1, 14.0, 12.4 ppm.

iv. N-[4-(Diethylamino)phenyl]-5,5'-dimethyl-[3,3'-biisoxazole]-4-carboxamide (**39o**)



To a solution of 5,5'-dimethyl-[3,3'-biisoxazole]-4-carboxylic acid **41o** (14.2 mg, 0.0683 mmol) in dry DMF (0.5 mL), *N*,*N*-diethyl-*p*-phenylenediamine **17** (11.8 µL, 0.0751 mmol, 1.1 equiv), HBTU (33.6 mg, 0.0887 mmol, 1.3 equiv), and DIPEA (23.8 µL, 137 mmol, 2.0 equiv) were added under argon. The reaction mixture was stirred at room temperature for 18 h. Diethyl ether (20 mL) was added, and the organic phase was washed with water (2 × 10 mL). The solvent was removed *in vacuo*, and the crude product mixture was subjected to a purification by an automated flash silica chromatography (*n*-hexane/EtOAc 1:0→0:1) to yield compound **39o** (0.0196 g, 0.0553 mmol, 81%). M.p. 117.5-119.2 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.87 (s, 1H), 7.53 (d, J = 9.1 Hz, 1H), 6.69 (d, J = 9.1 Hz, 2H), 6.62 (d, J = 1.1 Hz, 1H), 3.34 (q, J = 7.0 Hz, 4H), 2.88 (s, 3H), 2.55 (d, J = 0.9 Hz, 3H), 1.15 (t, J = 7.0 Hz, 6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.9, 170.7, 158.4, 155.6, 149.6, 145.4, 127.3, 122.4, 112.7, 111.5, 101.9, 44.8, 14.10, 12.7, 12.3 ppm. HRMS calc. for $C_{19}H_{23}N_4O_3$ $[M+H]^+$: 355.1770, found 355.1771.

_N_-[4-(Diethylamino)phenyl]-5-methyl-3-(5-methylthiophen-2-yl)isoxazole-4-carboxamide (39p)

i. (E/Z)-2-Methylthiophene-2-carbaldehyde oxime (**43p**)

To a solution of 5-methylthiophene-2-carbaldehyde **44p** (0.500 g, 3.96 mmol) in EtOH (10 mL), hydroxylamine hydrochloride (0.302 g, 4.36 mmol, 1.1 equiv) and pyridine (0.353 mL, 4.36 mmol, 1.1 equiv) were added. After stirring at room temperature for 4 h, the reaction mixture was quenched with a mixture of a saturated solution of NH_4Cl in H_2O (10 mL). The aqueous phase was extracted with dichloromethane (3 × 20 mL). The combined organic phases were dried with anhydrous Na_2SO_4, and the solvents were evaporated *in vacuo* to yield compound **43p** (542 mg, 97%) as a light orange solid. ^{1}H NMR (300 MHz, acetone-d_6) δ 11.14 (br, s, 1H, minor), 10.34 (br, s, 1H, major), 8.44 (d, J = 0.5 Hz, 1H, minor), 8.00 (d, J = 0.5 Hz, 1H, major), 7.97 (d, J = 0.6 Hz, 1H, major), 7.38 (d, J = 0.5 Hz, 1H, minor), 2.43 (s, 3H, minor), 2.41 (s, 3H, major) ppm. ^{13}C NMR (75 MHz, Acetone-d_6): δ 162.8, 161.5, 143.4, 141.5, 140.0, 138.5, 138.3, 136.2, 13.6, 13.4 ppm.

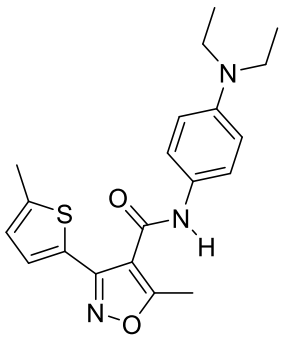
ii. Ethyl 5-methyl-3-(5-methylthiophen-2-yl)isoxazole-4-carboxylate (**45p**)

To a stirred solution of (*E/Z*)-2-methylthiophene-2-carbaldehyde oxime **43p** (0.100 g, 0.708 mmol), KCl (52.8 mg, 0.708 mmol) and Oxone® (326 mg, 1.1 mmol, 1.5 equiv) in H_2O (5 mL), ethyl 2-butynoate (0.206 mL, 1.77 mmol, 2.50 equiv) was added. The solution was stirred at room temperature for 5 h, and the aqueous phase was extracted with dichloromethane (3 × 20 mL). The combined organic phases were dried with anhydrous Na_2SO_4, and the solvents were evaporated *in vacuo*. The crude product mixture was subjected to a purification by an automated flash silica chromatography (*n*-hexane/EtOAc, 95:5) yielded compound **45p** (75.5 mg, 42%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.71 (d, ^3J = 3.6 Hz, 1H), 6.78 (dq, $^{3,4}J$ = 3.7, 1.0 Hz, 1H), 4.35 (q, ^3J = 7.1 Hz, 2H), 2.69 (s, 3H), 2.52 (d, ^4J = 1.1 Hz, 3H), 1.37 (t, ^3J = 7.1 Hz, 3H).

iii. 5-Methyl-3-(5-methylthiophen-2-yl)isoxazole-4-carboxylic acid (**41p**)

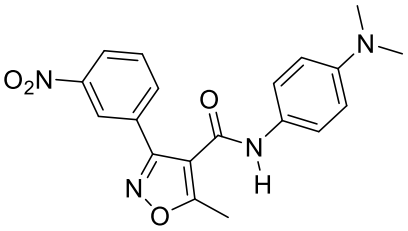
To a solution of ethyl 5-methyl-3-(5-methylthiophen-2-yl)isoxazole-4-carboxylate **45p** (94.0 mg, 0.374 mmol) in an equimixture of MeOH/H_2O (16 mL), NaOH (42.0 mg, 1.05 mmol, 2.8 equiv) was added. The reaction mixture was stirred at 60 °C for 20 h and then most of the MeOH was removed *in vacuo*. The aqueous layer was acidified with a 1 M solution of HCl in H_2O to pH 1, and then extracted with ethyl acetate (3 × 20 mL). The organic phase was washed with brine (20 mL), and the solvents were evaporated *in vacuo* to give compound **41p** (52.0 mg, 0.249 mmol, 66%). ^{1}H (NMR 300 MHz, DMSO-d_6): δ 13.30 (s, 1H), 7.78 (d, ^3J = 3.7 Hz, 1H), 6.89 (dq, $^{3,4}J$ = 3.7, 0.9 Hz, 1H), 2.66 (s, 3H), 2.49 (d, ^4J = 0.9 Hz, 3H).

iv. N-[4-(Diethylamino)phenyl]-5-methyl-3-(5-methylthiophen-2-yl)isoxazole-4-carboxamide (**39p**)



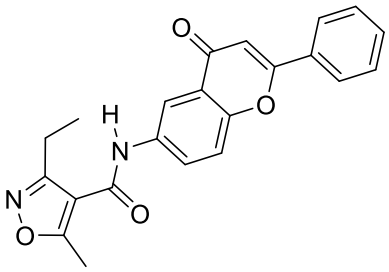
To a solution of 5-methyl-3-(5-methylthiophen-2-yl)isoxazole-4-carboxylic acid **41p** (0.0400 g, 0.179 mmol) in dry DMF (2 mL), *N*,*N*-diethyl-*p*-phenylenediamine **17** (32.7 µL, 0.20 mmol, 1.1 equiv), HBTU (88.3 mg, 0.233 mmol, 1.3 equiv), and DIPEA (62.4 µL, 0.358 mmol, 2.0 equiv) were added under argon. The reaction mixture was stirred at room temperature for 18 h. Diethyl ether (20 mL) was added, and the organic phase was washed with water (2 × 10 mL). The solvent was removed *in vacuo*, and the crude product mixture was subjected to a purification by an automated flash silica chromatography (*n*-hexane/EtOAc 1:0→0:1). Recrystallization (MeOH/H_2O 10:1) after the chromatographic purification gave compound **39p** (47.6 mg, 0.129 mmol, 72%). M.p. 161.5–162.2 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.16 (s, 1H), 7.44 (m$_c$, 2H), 7.42 (d, ^3J = 3.6 Hz, 1H), 6.86 (dd, $^{3,4}J$ = 3.7, 1.1 Hz, 1H), 6.66 (m$_c$, 2H), 3.31 (q, ^3J = 6.9 Hz, 4H), 2.52 (s, 3H), 2.47 (d, ^4J = 1.1 Hz, 3H), 1.07 (t, ^3J = 7.0 Hz, 6H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 169.2, 158.8, 154.9, 144.6, 142.5, 129.2, 127.1, 126.4, 126.3, 121.6, 112.8, 111.8, 43.8, 14.9, 12.4, 11.8 ppm. HRMS calc. for $C_{20}H_{24}N_3O_2S$ $[M+H]^+$: 370.1589, found 370.1588.

_N_-[4-(Dimethylamino)phenyl]-5-methyl-3-(3-nitrophenyl)isoxazole-4-carboxamide (40)



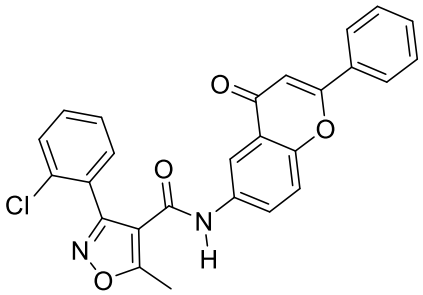
Synthesis according to the General procedure I. 5-Methyl-3-(3-nitrophenyl)isoxazole-4-carboxylic acid **41g** (58.0 mg, 0.234 mmol), *N*,*N*-dimethyl-*p*-phenylenediamine **42** (31.8 mg, 0.234 mmol), HBTU (115 mg, 0.304 mmol, 1.3 equiv), DIPEA (81.5 µL, 0.468 mmol, 2 equiv), DMF (2 mL). Solvent for extraction: diethyl ether. Recrystallization (MeOH/2-propanol/ethyl acetate/H_2O 30+20+10+1) after chromatography on silica gel gave compound **40** (67.0 mg, 0.183 mmol, 78%) as fine slightly orange needles. M.p. 202.2–203.9 °C (decomp.). ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.14 (s, 1H), 8.56 (dd≈t, 1H, ^4J = 2.0 Hz, ^4J = 2.0 Hz), 8.37 (ddd, 1H, ^3J = 8.3 Hz, ^4J = 1.0 Hz), 8.16 (ddd≈ddt, 1H, ^3J = 7.8 Hz), 7.82 (dd≈t, 1H), 7.42 (m$_c$, 2H), 6.71 (m$_c$, 2H), 2.86 (s, 6H), 2.62 (s, 3H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ170.4, 158.7, 158.6, 147.9, 147.7, 134.1, 130.5, 129.7, 127.8, 124.7, 122.4, 121.4, 113.4, 112.4, 40.3, 11.9 ppm. HRMS calc. for $C_{19}H_{19}N_4O_4$ $[M+H]^+$: 367.1406, found 367.1409.

3-Ethyl-5-methyl-*N*-(4-oxo-2-phenyl-4*H*-chromen-6-yl)isoxazole-4-carboxamide (SI50)



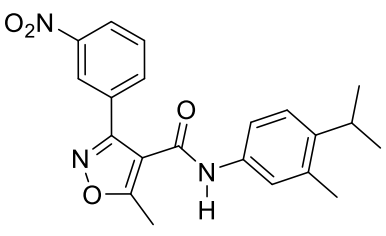
Synthesis according to the General procedure I. Deviating from the General procedure I, the reaction time was 4 d at room temperature. 3-Ethyl-5-methylisoxazole-4-carboxylic acid (50.0 mg, 0.322 mmol), 6-aminoflavone (76.5 mg, 0.322 mmol), HBTU (159 mg, 0.419 mmol, 1.3 equiv), DIPEA (0.112 mL, 0.644 mmol, 2 equiv), DMF (2 mL). Solvent for extraction: ethyl acetate and water containing 30% brine. Chromatography on silica gel gave compound **SI50** (78.9 mg, 0.211 mmol, 65%) as a yellowish solid. M.p. 197.9–198.7 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.40 (s, 1H), 8.42 (d, 1H, ^{4}J = 2.7 Hz), 8.15–8.09 (m, 2H), 8.06 (dd, 1H, ^{3}J = 9.1 Hz), 7.82 (d, 1H), 7.66–7.56 (m, 3H), 7.03 (s, 1H), 2.81 (q, 2H, ^{3}J = 7.5 Hz), 2.58 (s, 3H), 1.20 (t, 3H, ^{3}J = 7.5 Hz) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 176.8, 169.6, 163.2, 162.4, 160.3, 152, 136.1, 131.7, 131.1, 129.1, 126.4, 126.3, 123.5, 119.1, 114.2, 112.7, 106.5, 18.4, 12.1, 11.9 ppm. HRMS calc. for $C_{22}H_{19}N_2O_4$ $[M+H]^+$: 375.1345, found 375.1351.

3-(2-Chlorophenyl)-5-methyl-*N*-(4-oxo-2-phenyl-4*H*-chromen-6-yl)isoxazole-4-carboxamide (SI51)



Synthesis according to the General procedure I. Deviating from the General procedure I, the reaction time was 3 d at room temperature. 3-(2-Chlorophenyl)-5-methylisoxazole-4-carboxylic acid **41k** (47.9 mg, 0.202 mmol), 6-aminoflavone **5g** (47.8 mg, 0.202 mmol), HBTU (99.7 mg, 0.263 mmol, 1.3 equiv), DIPEA (70.4 μL, 0.404 mmol, 2 equiv), DMF (1 mL). Solvent for extraction: ethyl acetate and a mixture of water and brine (2:1). Chromatography on silica gel gave compound **S51** (32.8 mg, 0.0718 mmol, 36%) as a yellow solid. M.p. 241.2–244.4 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.44 (s, 1H), 8.29 (d, 1H, ^{4}J = 2.7 Hz), 8.13–8.07 (m, 2H), 7.94 (dd, 1H, ^{3}J = 9.1 Hz, ^{4}J = 2.7 Hz), 7.78 (d, 1H, ^{3}J = 9.1 Hz), 7.65–7.46 (m, 7H), 7.02 (s, 1H), 2.71 (s, 3H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 176.8, 169.9, 162.4, 159.9, 159.6, 152.0, 136.0, 132.3, 131.8, 131.6, 131.1, 129.6, 129.1, 127.4, 127.3, 126.4, 126.3, 123.4, 119.1, 114.2,106.5, 12.3 ppm. HRMS calc. for $C_{26}H_{18}ClN_2O_4$ $[M+H]^+$: 457.0955, found 457.0956.

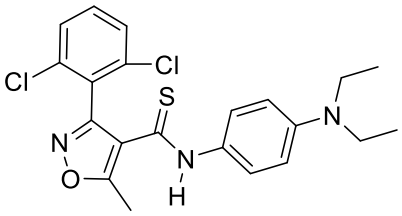
***N*-(4-Isopropyl-3-methylphenyl)-5-methyl-3-(3-nitrophenyl)isoxazole-4-carboxamide (SI52)**



Synthesis according to the General procedure I. 5-Methyl-3-(3-nitrophenyl)isoxazole-4-carboxylic acid **41g** (66.8 mg, 0.269 mmol), 4-isopropyl-3-methylaniline hydrochloride (50.0 mg, 0.269 mmol), HBTU (133 mg, 0.350 mmol, 1.3 equiv), DIPEA (0.141 mL, 0.807 mmol, 2 equiv), DMF (1.5 mL). Solvent for extraction: diethyl ether. Recrystallization (EtOH/H_2O 10+1) without chromatography on silica gel gave compound **SI52** (83.2 mg, 0.219 mmol, 82%) as fine white needles. M.p. 181.3–

182.4 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.30 (s, 1H), 8.55 (dd≈bs, 1H), 8.36 (ddd, 1H, ^{3}J = 8.3 Hz, ^{4}J = 2.4 Hz, ^{4}J = 1.0 Hz), 8.15 (ddd≈bd, 1H, ^{3}J = 7.8 Hz), 7.81 (dd≈t, 1H), 7.45–7.34 (m, 2H), 7.19 (d, 1H), 3.06 (sept, 1H, ^{3}J = 6.8 Hz), 2.62 (s, 3H), 2.27 (s, 3H), 1.16 (d, 6H, ^{3}J = 6.8 Hz) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 170.7, 159.2, 158.6, 147.9, 142.5, 135.6, 134.9, 134.1, 130.6, 129.6, 124.8, 124.7, 122.3, 121.6, 118.0, 113.3, 28.3, 23.0, 18.9, 12.0 ppm. HRMS calc. for $C_{21}H_{22}N_3O_4$ $[M+H]^+$: 380.1610, found 380.1614.

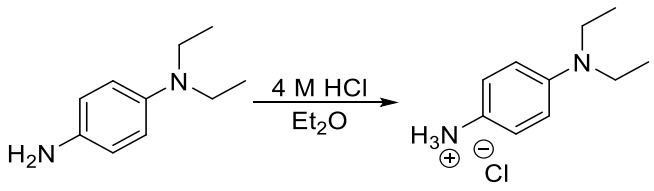
3-(2,6-Dichlorophenyl)-*N*-[4-(diethylamino)phenyl]-5-methylisoxazole-4-carbothioamide (SI53)



Synthesis according to the General procedure V. 3-(2,6-Dichlorophenyl)-*N*-[4-(diethylamino)phenyl]-5-methylisoxazole-4-carboxamide **39e** (0.100 g, 0.239 mmol), Lawesson's reagent (58.0 mg, 0.143 mmol, 0.6 equiv), toluene (2 mL). Reaction time: 6 h. Recrystallization (EtOH) after chromatography on silica gel gave compound **SI53** (76.0 mg, 0.175 mmol, 73%) as yellow crystals. M.p. 155.7–158.9 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.49 (s, 1H), 7.62 – 7.45 (m, 5H), 6.65 (m_c, 2H), 3.33 (q, 4H, ^{3}J = 7.0 Hz), 2.62 (s, 3H), 1.08 (t, 6H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 182.7, 164.4, 158.2, 145.8, 134.8, 131.7, 128.2, 128.1, 127.6, 124.4, 110.7, 109.5, 43.7, 12.3, 12.0 ppm. HRMS calc. for $C_{21}H_{22}Cl_2N_3OS$ $[M+H]^+$: 434.0861, found 434.0862.

Preparation of compounds in Table 1 and other related compounds

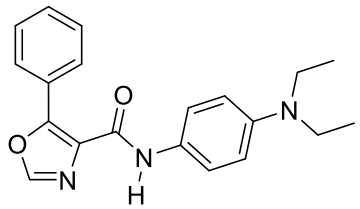
N,*N*-Diethyl-*p*-phenylenediamine hydrochloride (50)



17 **50**

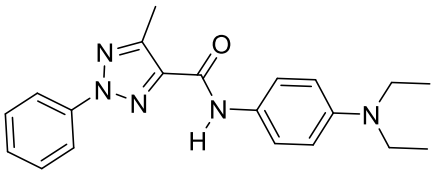
N,*N*-Diethyl-*p*-phenylenediamine **17** (4.77 mL, 29.0 mmol) was dissolved in diethyl ether (13 mL). A 4 M solution of hydrochloric acid in 1,4-dioxane (7 mL) was added. The mixture was stirred for 2 h at room temperature. The solvent was removed with a rotary evaporator. The residue was treated with methanol and the solvent was removed with a rotary evaporator to give a solid material, which was recrystallized from 2-propanol, filtered and washed with ethyl acetate to give compound **50** (3.00 g, 14.9 mmol, 51%) as brownish white crystals, which was used without further purification or characterization.

***N*-[4-(Diethylamino)phenyl]-5-phenyloxazole-4-carboxamide (47a)**



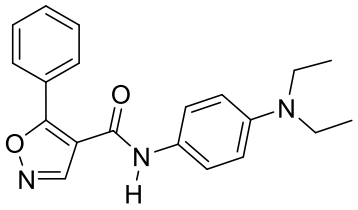
Synthesis according to the General procedure I. Deviating from the General procedure I, the reaction mixture was diluted with ethyl acetate for the work-up and extracted once with a 2 M solution of sodium hydroxide in water and twice with 4 M hydrochloric acid. The combined hydrochloric acid phases were made alkaline with a 2 M solution of sodium hydroxide in water and extracted twice with ethyl acetate. The combined organic phases were washed twice with a mixture of water and brine (10:1). 5-Phenyl-1,3-oxazole-4-carboxylic acid (50.0 mg, 0.264 mmol), *N*,*N*-diethyl-*p*-phenylenediamine hydrochloride **50** (62.4 mg, 0.311 mmol, 1.2 equiv), HBTU (0.300 g, 0.792 mmol, 3 equiv), DIPEA (0.230 mL, 1.32 mmol, 5 equiv), DMF (2.5 mL). Recrystallization (twice with MeOH/H_2O 10+1) [without chromatography on silica gel] gave compound **47a** (56.0 mg, 0.167 mmol, 63%) as greenish plates. M.p. 85.1–88.4 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.86 (s, 1H), 8.64 (s, 1H,), 8.21–8.15 (m, 2H), 7.60–7.45 (m, 5H,), 6.64 (m_c, 2H), 3.31 (q, 4H, ^3J = 7.0 Hz), 1.08 (t, 6H, ^3J = 7.0 Hz) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 158.6, 151.1, 150.1, 144.4, 129.8, 129.3, 128.4, 127.7, 126.9, 126.9, 122.2, 111.6, 43.7, 12.4 ppm. HRMS calc. for $C_{20}H_{22}N_3O_2$ $[M+H]^+$: 336.1712, found 336.1711.

***N*-[4-(Diethylamino)phenyl]-5-methyl-2-phenyl-2*H*-1,2,3-triazole-4-carboxamide (47b)**



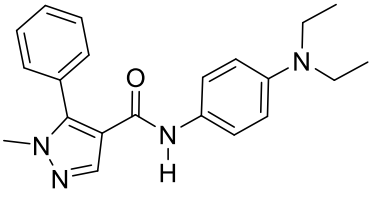
Synthesis according to the General procedure I. Deviating from the General procedure I, the reaction mixture was diluted with diethyl ether for the work-up and washed with water, a 2 M solution of sodium hydroxide in water and twice with water. 5-Methyl-2-phenyl-2*H*-1,2,3-triazole-4-carboxylic acid **46b** (102 mg, 0.500 mmol), *N*,*N*-diethyl-*p*-phenylenediamine hydrochloride **50** (118 mg, 0.588 mmol, 1.2 equiv), HBTU (284 mg, 0.750 mmol, 1.5 equiv), DIPEA (0.348 mL, 2.00 mmol, 4 equiv), DMF (3 mL). Recrystallization (MeOH/H_2O 10+1) after chromatography on silica gel gave compound **47b** (137 mg, 0.392 mmol, 78%) as fine greenish crystals. M.p. 112.2–114.1 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.06 (s, 1H), 8.15–8.08 (m, 2H), 7.65–7.43 (m, 5H), 6.70–6.62 (m, 2H), 3.32 (q, 4H, ^3J = 7.0 Hz), 2.57 (s, 3H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 158.1, 146.8, 144.5, 140.8, 138.8, 129.7, 128.2, 126.8, 122.3, 118.7, 111.6, 43.7, 12.4, 11.1 ppm. HRMS calc. for $C_{20}H_{24}N_5O$ $[M+H]^+$: 350.1981, found 350.1980.

_N_-[4-(Diethylamino)phenyl]-5-phenylisoxazole-4-carboxamide (47d)



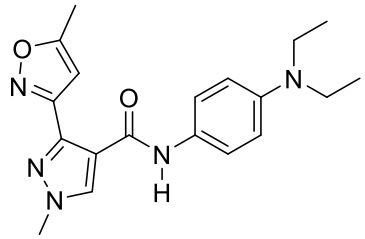
Synthesis according to the General procedure I. Deviating from the General procedure I, the reaction mixture was diluted with diethyl ether for the work-up and washed twice with water, twice with a 2 M solution of sodium hydroxide in water and twice with water. 5-Phenylisoxazole-4-carboxylic acid **46d** (189 mg, 1.00 mmol), *N*,*N*-diethyl-*p*-phenylenediamine hydrochloride **50** (283 mg, 1.41 mmol, 1.4 equiv), HBTU (569 mg, 1.50 mmol, 1.5 equiv), DIPEA (0.697 mL, 4.00 mmol, 4 equiv), DMF (5 mL). Automated chromatography on silica gel gave compound **47d** (136 mg, 0.405 mmol, 41%) as a brown-yellow resin. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.06 (s, 1H), 9.04 (s, 1H), 8.02–7.95 (m, 2H), 7.58–7.52 (m, 3H), 7.44 (m$_c$, 2H), 6.66 (m$_c$, 2H), 3.31 (q, 4H, ^{3}J = 7.0 Hz), 1.08 (t, 6H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 167.4, 158.2, 151.0, 144.5, 130.9, 128.7, 127.8, 127.0, 126.3, 121.9, 112.9, 111.7, 43.7, 12.3 ppm. HRMS calc. for $C_{20}H_{22}N_3O_2$ $[M+H]^+$: 336.1712, found 336.1711.

_N_-[4-(Diethylamino)phenyl]-1-methyl-5-phenyl-1*H*-pyrazole-4-carboxamide (47e)



Synthesis according to the General procedure I. 1-Methyl-5-phenyl-1*H*-pyrazole-4-carboxylic acid **46e** (101 mg, 0.500 mmol), *N*,*N*-diethyl-*p*-phenylenediamine **17** (83.1 µL, 0.500 mmol), HBTU (247 mg, 0.650 mmol, 1.3 equiv), DIPEA (0.174 mL, 1.00 mmol, 2 equiv), DMF (1.5 mL). Solvent for extraction: diethyl ether. Automated chromatography on silica gel gave compound **47e** (92.1 mg, 0.264 mmol, 53%) as a white solid. M.p. 151.0–153.4 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.32 (s, 1H), 8.07 (s, 1H), 7.53–7.42 (m, 5H), 7.33 (m$_c$, 2H), 6.58 (m$_c$, 2H), 3.68 (s, 3H), 3.27 (q, 4H, ^{3}J = 7.0 Hz), 1.04 (t, 6H, ^{3}J = 7.1 Hz) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 160.1, 144.0, 143.4, 137.8, 130.4, 129.2, 128.7, 128.0, 127.8, 121.8, 116.4, 111.8, 43.7, 37.0, 12.3 ppm. HRMS calc. for $C_{21}H_{25}N_4O$ $[M+H]^+$: 349.2028, found 349.2026.

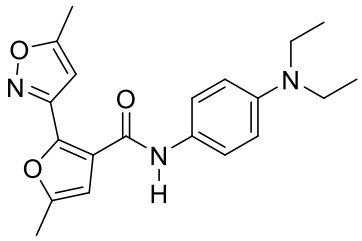
_N_-[4-(Diethylamino)phenyl]-1-methyl-3-(5-methylisoxazol-3-yl)-1*H*-pyrazole-4-carboxamide (47f)



Synthesis according to the General procedure I. 1-Methyl-3-(5-methylisoxazol-3-yl)-1*H*-pyrazole-4-carboxylic acid **46f** (5.0 mg, 0.024 mmol), *N*,*N*-diethyl-*p*-phenylenediamine **17** (6.0 µL, 0.036 mmol, 1.5 equiv), HBTU (12 mg, 0.031 mmol, 1.3 equiv), DIPEA (8.4 µL, 0.048 mmol, 2 equiv), DMF (0.5 mL). Solvent for extraction: diethyl ether. Eluent for purification: MeOH/DCM 1:9. Chromatography on silica gel gave compound **47f** (6.4 mg, 0.18 mmol, 75%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.25 (s, 1H), 8.17 (s, 1H), 7.60 (m$_c$, 2H), 6.69 (m$_c$, 2H), 6.55 (d, ^{4}J = 0.9 Hz, 1H), 3.96 (s, 3H), 3.33 (q, ^{3}J = 7.0 Hz, 4H), 2.51 (d, ^{4}J = 0.9 Hz, 3H), 1.15 (t, ^{3}J = 7.0 Hz,

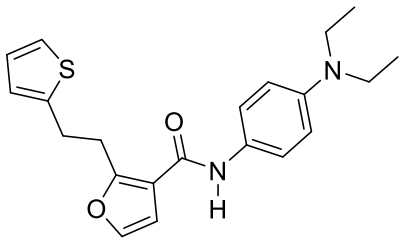
6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.6, 159.3, 158.5, 145.0, 137.4, 137.1, 128.2, 122.1, 119.4, 112.9, 101.4, 44.8, 39.7, 12.7, 12.3 ppm. HRMS calc. for $C_{19}H_{24}N_5O_2$ $[M+H]^+$: 354.1930, found 354.1930.

N-[4-(Diethylamino)phenyl]-5-methyl-2-(5-methylisoxazol-3-yl)furan-3-carboxamide (47h)



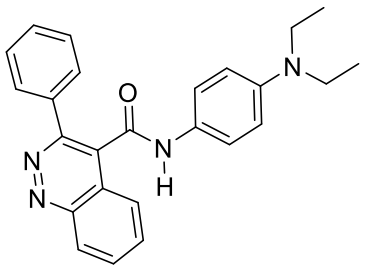
Synthesis according to the General procedure I. 5-Methyl-2-(5-methylisoxazol-3-yl)furan-3-carboxylic acid **46h** (5.0 mg, 0.024 mmol), *N*,*N*-diethyl-*p*-phenylenediamine **17** (6.0 µL, 0.036 mmol, 1.5 equiv), HBTU (12 mg, 0.031 mmol, 1.3 equiv), DIPEA (8.2 µL, 0.048 mmol, 2 equiv), DMF (0.5 mL). Solvent for extraction: diethyl ether. Eluent for purification: *n*-heptane/EtOAc 4:1. Chromatography on silica gel gave compound **47h** (6.4 mg, 0.181 mmol, 75%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.25 (s, 1H), 8.17 (s, 1H), 7.60 (m_c, 2H), 6.69 (m_c, 2H), 6.55 (d, ^4J = 0.9 Hz, 1H), 3.96 (s, 3H), 3.33 (q, ^3J = 7.0 Hz, 4H), 2.51 (d, ^4J = 0.9 Hz, 3H), 1.15 (t, ^3J = 7.0 Hz, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.6, 159.3, 158.5, 145.0, 137.4, 137.1, 128.2, 122.1, 119.4, 112.9, 101.4, 44.8, 39.7, 12.7, 12.3 ppm. HRMS calc. for $C_{20}H_{24}N_3O_3$ $[M+H]^+$: 354.1818, found 354.1818.

N-[4-(Diethylamino)phenyl]-2-[2-(thiophen-2-yl)ethyl]furan-3-carboxamide (47i)



Synthesis according to the General procedure I. Deviating from the General procedure I, the reaction time was 3 d. 2-[2-(Thiophen-2-yl)ethyl]furan-3-carboxylic acid **46i** (25.0 mg, 0.112 mmol), *N*,*N*-diethyl-*p*-phenylenediamine **17** (18.7 µL, 0.112 mmol), HBTU (60.1 mg, 0.159 mmol, 1.3 equiv), DIPEA (39.0 µL, 0.224 mmol, 2 equiv), DMF (1 mL). Solvent for extraction: diethyl ether. Chromatography on silica gel gave compound **47i** (38.4 mg, 0.104 mmol, 93%) as a greyish resin. M.p. 89.9–91.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34–7.28 (m, 3H), 7.10 (dd, 1H, J = 1.2 Hz, J = 5.1 Hz), 7.07 (bs, 1H), 6.90 (dd, 1H, J = 3.4 Hz), 6.79 (m_c, 1H), 6.65 (m_c, 2H), 6.52 (bs, 1H), 3.42–3.22 (m, 8H), 1.15 (t, 6H, J = 7.0 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.8, 158.7, 145.6 , 143.6, 141.0, 127.0, 126.4, 124.9, 123.6, 122.9, 117.2, 112.6, 108.7, 44.7, 29.9, 28.3, 12.7 ppm. HRMS calc. for $C_{21}H_{25}N_2O_2S$ $[M+H]^+$: 369.1637, found 369.1639.

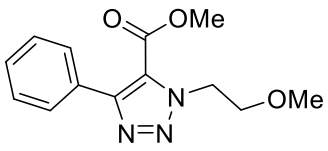
_N_-[4-(Diethylamino)phenyl]-3-phenylcinnoline-4-carboxamide (47j)



Synthesis according to the General procedure I. 3-Phenylcinnoline-4-carboxylic acid **46j** (53.6 mg, 0.214 mmol), *N*,*N*-diethyl-*p*-phenylenediamine **17** (35.6 μL, 0.214 mmol), HBTU (106 mg, 0.278 mmol, 1.3 equiv), DIPEA (74.5 μL, 0.428 mmol, 2 equiv), DMF (1 mL). Solvent for extraction: diethyl ether. Recrystallization (EtOH/water 10+1) after chromatography on silica gel gave compound **47j** (30.6 mg, 0.0772 mmol, 36%) as yellow needles. M.p. 246.3–249.9 °C (decomp). ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.40 (s, 1H), 8.62 (m$_c$, 1H), 8.07–7.93 (m, 5H), 7.59–7.47 (m, 3H), 7.32 (m$_c$, 2H), 6.63 (m$_c$, 2H), 3.30 (q, 4H, ^{3}J = 7.0 Hz), 1.07 (t, 6H, ^{3}J = 7.0 Hz) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 162.5, 149.4, 148.8, 144.8, 136.8, 132.7, 131.2, 129.2, 129.0, 128.4, 128.2, 126.6, 124.5, 122.3, 121.8, 111.7, 43.7, 12.3 ppm. HRMS calc. for $C_{25}H_{25}N_4O$ $[M+H]^+$: 397.2028, found 397.2033.

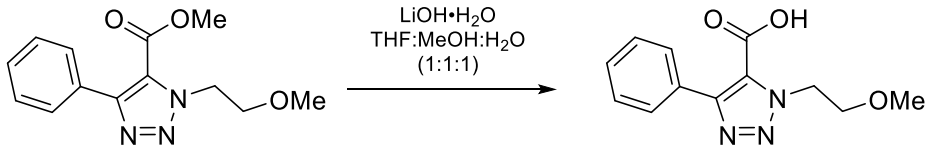
1-(2-Methoxyethyl)-4-phenyl-1*H*-1,2,3-triazole-5-carboxylic acid (46k)

i. Methyl 1-(2-methoxyethyl)-4-phenyl-1H-1,2,3-triazole-5-carboxylate (**SI54**)



Synthesis according to the General procedure VIII, method B. Methyl phenylpropiolate (0.160 g, 1.00 mmol), 1-bromo-2-methoxyethane (94.0 μL, 1.00 mmol), sodium azide (65.0 mg, 1.00 mmol), Solvent volume (2.5 mL). reaction conditions: first overnight at room temperature and then 70 min, 140 °C. Chromatography on silica gel gave compound **SI54** (121 mg, 0.463 mmol, 46%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.89–7.81 (m, 2H), 7.48–7.38 (m, 3H), 4.68 (t, 2H, ^{3}J = 5.7 Hz), 3.97 (t, 2H, ^{3}J = 5.7 Hz), 3.92 (s, 3H), 3.36 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.8, 150.3, 135.7, 129.6, 129.4, 129.3, 128.3, 70.2, 59.1, 55.5, 52.4 ppm. HRMS calc. for $C_{13}H_{16}N_3O_3$ $[M+H]^+$: 262.1192, found 262.1190.

ii. 1-(2-Methoxyethyl)-4-phenyl-1H-1,2,3-triazole-5-carboxylic acid (**46k**)

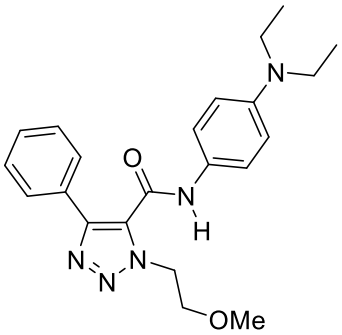


SI54 **46k**

A mixture of methyl 1-(2-methoxyethyl)-4-phenyl-1*H*-1,2,3-triazole-5-carboxylate **SI54** (99.7 mg, 0.382 mmol) and lithum hydroxide monohydrate (24.0 mg, 0.572 mmol, 1.5 equiv) in an equimixture of THF, methanol and water (1.50 mL) was stirred for 2 d at room temperature. The reaction mixture was diluted with ethyl acetate and transferred to a separatory funnel. Water was added, and the mixture was acidified with 1 M hydrochloric acid. The phases were separated, the organic phase was washed neutral with three portions of water and the solvent was removed with a rotary evaporator to give compound **46k** (83.3 mg, 0.337 mmol, 88%) as a brownish solid. The product was used as such

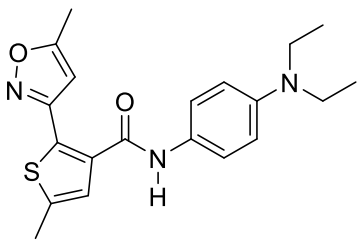
in next step without further purification. M.p. 114.0–114.3 °C. HRMS calc. for $C_{12}H_{14}N_3O_3$ $[M+H]^+$: 248.1035, found 248.1037.

N-[4-(Diethylamino)phenyl]-1-(2-methoxyethyl)-4-phenyl-1*H*-1,2,3-triazole-5-carboxamide (47k)



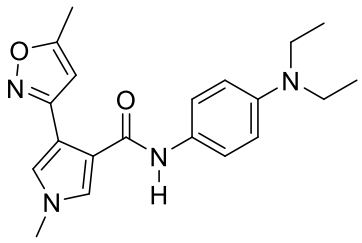
Synthesis according to the General procedure I. 1-(2-Methoxyethyl)-4-phenyl-1*H*-1,2,3-triazole-5-carboxylic acid **46k** (40.5 mg, 0.164 mmol), *N*,*N*-diethyl-*p*-phenylenediamine **17** (27.2 μL, 0.164 mmol), HBTU (80.9 mg, 0.213 mmol, 1.3 equiv), DIPEA (57.1 μL, 0.328 mmol, 2 equiv), DMF (1.5 mL). Solvent for extraction: diethyl ether and a mixture of water with 20% brine. Chromatography on silica gel gave compound **47k** (52.4 mg, 0.133 mmol, 81%) as a brownish oil. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.14 (s, 1H), 7.90–7.85 (m, 2H), 7.54–7.37 (m, 5H), 6.64 (m$_c$, 2H), 4.69 (t, 2H, J = 5.3 Hz), 3.93 (t, 2H, J = 5.3 Hz), 3.31 (q, 4H, J = 7.0 Hz), 3.28 (s, 3H), 1.07 (t, 6H, J = 7.0 Hz) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 158.7, 145.7, 144.4, 139.5, 129.6, 128.6, 128.3, 128.0, 127.0, 122.0, 111.7, 69.5, 57.9, 54.5, 43.7, 12.3 ppm. HRMS calc. for $C_{22}H_{28}N_5O_2$ $[M+H]^+$: 394.2243, found 394.2246.

N-[4-(Diethylamino)phenyl]-5-methyl-2-(5-methylisoxazol-3-yl)thiophene-3-carboxamide (47l)



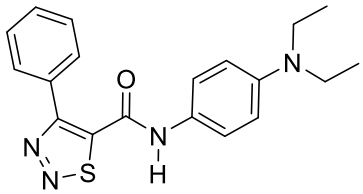
Synthesis according to the General procedure I. 5-Methyl-2-(5-methylisoxazol-3-yl)thiophene-3-carboxylic acid **46l** (5.0 mg, 0.022 mmol), *N*,*N*-diethyl-*p*-phenylenediamine **17** (5.6 μL, 0.034 mmol, 1.5 equiv), HBTU (11 mg, 0.029 mmol, 1.3 equiv), DIPEA (7.8 μL, 0.045 mmol, 2 equiv), DMF (0.5 mL). Solvent for extraction: diethyl ether. Eluent for purification: *n*-heptane/EtOAc, 4:1. Chromatography on silica gel gave compound **47l** (5.3 mg, 0.14 mmol, 64%) as a light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.81 (s, 1H), 7.51 (d, ^3J = 8.9 Hz, 2H), 7.34 (m$_c$, 1H), 6.68 (d, ^3J = 9.0 Hz, 2H), 6.27 (d, ^4J = 0.9 Hz, 1H), 3.33 (q, ^3J = 7.1 Hz, 4H), 2.50 (d, ^4J = 1.1 Hz, 3H), 2.46 (d, ^4J = 0.9 Hz, 3H), 1.15 (t, ^3J = 7.0 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.22, 160.67, 157.45, 145.26, 141.03, 137.30, 130.01, 127.43, 126.45, 122.17, 112.61, 102.90, 44.74, 15.29, 12.69, 12.38. HRMS calc. for $C_{20}H_{24}N_3O_3$ $[M+H]^+$: 370.1587, found 370.1588.

_N_-[4-(Diethylamino)phenyl]-1-methyl-4-(5-methylisoxazol-3-yl)-1_H_-pyrrole-3-carboxamide (47m)



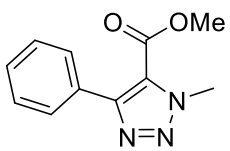
Synthesis according to the General procedure I. 1-Methyl-4-(5-methylisoxazol-3-yl)-1*H*-pyrrole-3-carboxylic acid **46m** (5.0 mg, 0.024 mmol), *N*,*N*-diethyl-*p*-phenylenediamine **17** (8.1 μL, 0.049 mmol, 2.0 equiv), HATU (14 mg, 0.036 mmol, 1.5 equiv), DIPEA (8.5 μL, 0.049 mmol, 2 equiv), DMF (0.5 mL). Solvent for extraction: diethyl ether. Eluent for purification: MeOH/DCM, 1:9. Chromatography on silica gel gave compound **47m** (7.1 mg, 0.020 mmol, 84%) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.19 (s, 1H), 7.61 (d, J = 8.6 Hz, 2H), 7.55 (d, J = 2.7 Hz, 1H), 6.93 (d, J = 2.7 Hz, 1H), 6.70 (d, J = 8.5 Hz, 2H), 6.12 (d, J = 1.0 Hz, 1H), 3.71 (s, 3H), 3.32 (q, J = 7.0 Hz, 4H), 2.46 (d, J = 0.9 Hz, 3H), 1.14 (t, J = 7.0 Hz, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.79, 161.32, 158.46, 144.61, 130.46, 128.83, 124.55, 121.87, 119.29, 113.00, 109.64, 100.68, 44.72, 36.77, 12.55, 12.09 ppm. HRMS calc. for $C_{20}H_{24}N_3O_3$ $[M+H]^+$: 353.1983, found 353.1981.

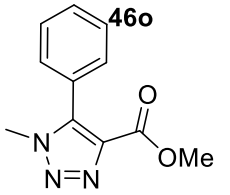
_N_-[4-(Diethylamino)phenyl]-4-phenyl-1,2,3-thiadiazole-5-carboxamide (47n)



Synthesis according to the General procedure I. 4-Phenyl-1,2,3-thiadiazole-5-carboxylic acid **46n** (50.0 mg, 0.242 mmol), *N*,*N*-diethyl-*p*-phenylenediamine **17** (40.3 μL, 0.242 mmol), HBTU (119 mg, 0.315 mmol, 1.3 equiv), DIPEA (84.3 μL, 0.484 mmol, 2 equiv), DMF (1.5 mL). Solvent for extraction: diethyl ether. Automated chromatography on silica gel gave compound **47n** (40.9 mg, 0.116 mmol, 48%) as a brown resin. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.62 (s, 1H), 7.96–7.89 (m, 2H), 7.60–7.46 (m, 3H), 7.39 (m$_c$, 2H), 6.65 (m$_c$, 2H), 3.31 (q, 4H, ^{3}J = 7.0 Hz), 1.07 (t, 6H, ^{3}J = 7.0 Hz) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 158.6, 156.7, 145.0, 144.9, 130.1, 129.5, 129.0, 128.0, 126.5, 121.6, 111.6, 43.7, 12.3 ppm. HRMS calc. for $C_{19}H_{21}N_4OS$ $[M+H]^+$: 353.1436, found 353.1434.

Methyl 1-methyl-4-phenyl-1_H_-1,2,3-triazole-5-carboxylate (46o) and methyl 1-methyl-5-phenyl-1_H_-1,2,3-triazole-4-carboxylate (46p)





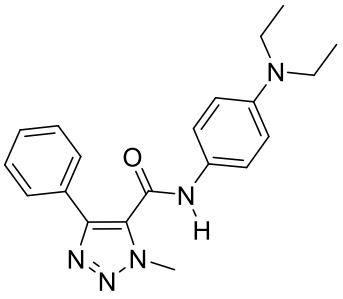
46o

46p

Synthesis according to the General procedure VIII, method B. Methyl phenylpropiolate (0.160 g, 1.00 mmol), iodomethane (62.3 μL, 1.00 mmol), sodium azide (65.0 mg, 1.00 mmol). Solvent volume: 2.5 mL. Reaction conditions: first overnight at room temperature, then 160 min 130 °C. Chromatography on silica gel gave compound **46o** (35.0 mg, 0.161 mmol, 16%) as a white solid and **46p** (37.1 mg, 0.171 mmol, 17%) as a colorless resin. Both compounds were slightly impure and used in the next step without further purification. Compound **46o**: M.p. 139-145 °C (decomp.). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.76–7.68 (m, 2H), 7.50–7.38 (m, 3H), 4.35 (s, 3H), 3.87 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.7, 150.6, 129.5, 129.1, 128.2, 52.5, 38.5 ppm.

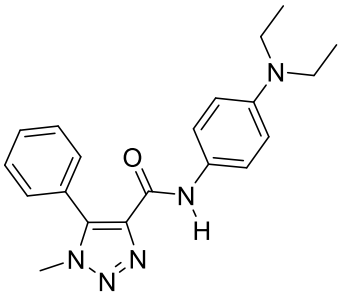
HRMS calc. for $C_{11}H_{12}N_3O_2$ $[M+H]^+$: 218.0930, found 218.0936. Compound **46p**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.57–7.48 (m, 3H), 7.46–7.34 (m, 2H), 3.95 (s, 3H), 3.86 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ161.6, 148.2, 141.6, 136.6, 130.4, 129.8, 129.0, 128.9, 125.9, 52.1, 35.6 ppm. HRMS calc. for $C_{11}H_{12}N_3O_2$ $[M+H]^+$: 218.0930, found 218.0930.

N-[4-(Diethylamino)phenyl]-1-methyl-4-phenyl-1*H*-1,2,3-triazole-5-carboxamide (47o)



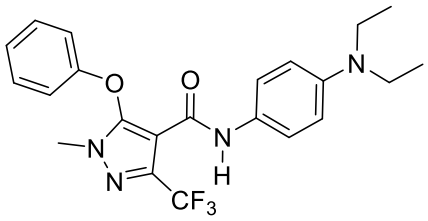
Synthesis according to the General procedure VI. Methyl 1-methyl-4-phenyl-1*H*-1,2,3-triazole-5-carboxylate **46o** (33.8 mg, 0.156 mmol), $LiOH{\cdot}H_2O$ (9.80 mg, 0.233 mmol, 1.5 equiv). solvent volume: 300 μL each. *N*,*N*-diethyl-*p*-phenylenediamine **17** (25.9 μL, 0.156 mmol), HBTU (76.9 mg, 0.203 mmol, 1.3 equiv), DIPEA (54.3 μL, 0.312 mmol, 2 equiv), DMF (1 mL). Solvent for extraction: diethyl ether. Recrystallization (EtOH) after chromatography on silica gel gave compound **47o** (12.4 mg, 0.0355 mmol, 23%) as a white solid. M.p. 167.5–171.1 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ10.54 (s, 1H), 7.80–7.75 (m, 2H), 7.50–7.34 (m, 5H), 6.67 (m_c, 2H), 4.11 (s, 3H), 3.32 (q, 4H, ^3J = 7.0 Hz), 1.08 (t, 6H, ^3J = 7.0 Hz) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ156.7, 144.9, 143.4, 130.4, 130.1, 128.7, 128.2, 126.4, 126.2, 121.6, 111.7, 43.7, 35.6, 12.3 ppm. HRMS calc. for $C_{20}H_{24}N_5O$ $[M+H]^+$: 350.1981, found 350.1981.

N-[4-(Diethylamino)phenyl]-1-methyl-5-phenyl-1*H*-1,2,3-triazole-4-carboxamide (47p)



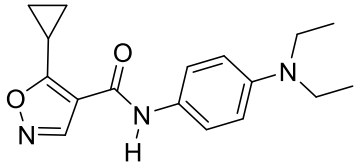
Synthesis according to the General procedure VI. Methyl 1-methyl-5-phenyl-1*H*-1,2,3-triazole-4-carboxylate **46p** (36.5 mg, 0.168 mmol), $LiOH{\cdot}H_2O$ (10.6 mg, 0.252 mmol, 1.5 equiv). Solvent volume: 0.300 mL each. *N*,*N*-diethyl-*p*-phenylenediamine **17** (27.9 μL, 0.168 mmol), HBTU (82.8 mg, 0.218 mmol, 1.3 equiv), DIPEA (58.5 μL, 0.336 mmol, 2 equiv), DMF (1 mL). Solvent for extraction: diethyl ether. Chromatography on silica gel gave compound **47p** (22.7 mg, 0.0650 mmol, 39%) as a brownish resin. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.00 (s, 1H), 7.60–7.48 (m, 7H), 6.60 (m_c, 2H), 3.95 (s, 3H), 3.29 (q, 4H, ^3J = 7.0 Hz), 1.06 (t, 6H, ^3J = 7.0 Hz) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ157.8, 144.2, 139.0, 138.5, 130.0, 129.4, 128.1, 127.2, 126.0, 121.9, 111.7, 43.7, 35.4, 12.3 ppm. HRMS calc. for $C_{20}H_{24}N_5O$ $[M+H]^+$: 350.1981, found 350.1982.

_N_-[4-(Diethylamino)phenyl]-1-methyl-5-phenoxy-3-(trifluoromethyl)-1_H_-pyrazole-4-carboxamide (47q)



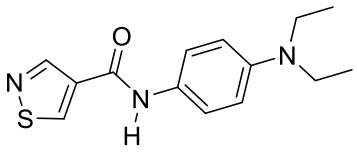
Synthesis according to the General procedure I. 1-Methyl-5-phenoxy-3-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid **46q** (25.0 mg, 0.0873 mmol), *N*,*N*-diethyl-*p*-phenylenediamine **17** (14.5 μL, 0.0873 mmol), HBTU (43.0 mg, 0.113 mmol, 1.3 equiv), DIPEA (30.4 μL, 0.175 mmol, 2 equiv), DMF (1 mL). Solvent for extraction: diethyl ether. Chromatography on silica gel gave compound **47q** (34.1 mg, 0.0789 mmol, 90%) as a white solid. M.p. 152.8–154.2 °C (decomp.). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54 (s, 1H), 7.44–7.36 (m, 2H), 7.23–7.14 (m, 3H), 7.01 (m_c, 2H), 6.56 (m_c, 2H), 3.71 (s, 3H), 3.29 (q, 4H, ^3J = 7.0 Hz), 1.10 (t, 6H, ^3J = 7.0 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.7, 155.7, 147.9, 145.6, 140.2 (q, J = 38.6 Hz), 130.8, 126.1, 125.2, 122.4, 120.2 (q, J = 269.8 Hz), 115.4, 112.4, 105.3 , 44.7, 35.7, 12.6 ppm. HRMS calc. for $C_{22}H_{24}F_3N_4O_2$ $[M+H]^+$: 433.1851, found 433.1860.

5-Cyclopropyl-_N_-[4-(diethylamino)phenyl]isoxazole-4-carboxamide (47r)



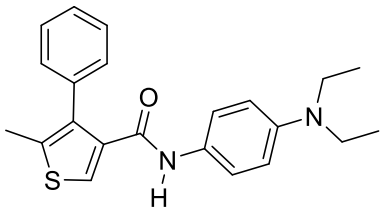
Synthesis according to the General procedure I. 5-Cyclopropylisoxazole-4-carboxylic acid **46r** (153 mg, 1.00 mmol), *N*,*N*-diethyl-*p*-phenylenediamine **17** (0.166 mL, 1.00 mmol), HBTU (493 mg, 1.30 mmol, 1.3 equiv), DIPEA (0.348 mL, 2.00 mmol, 2 equiv), DMF (2 mL). Solvent for extraction: diethyl ether. Chromatography on silica gel gave an oil that was crystallized on cooling its solution in MeOH/H_2O (20+1) in a refrigerator to yield compound **47r** (41.0 mg, 0.137 mmol, 14%) as slightly pink needles. M.p. 132.1–140.0 °C (decomp.). ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.68 (s, 1H), 9.00 (s, 1H), 7.43 (m_c, 2H), 6.66 (m_c, 2H), 3.31 (q, 4H, ^3J = 7.0 Hz), 2.99–2.89 (m, 1H), 1.24–1.05 (m, 10H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 175.7, 158.5, 149.1, 144.4, 126.9, 122.3, 111.8, 111.7, 43.7, 12.3, 9.5, 8.1 ppm. HRMS calc. for $C_{17}H_{22}N_3O_2$ $[M+H]^+$: 300.1712, found 300.1716.

***N*-[4-(Diethylamino)phenyl]isothiazole-4-carboxamide (47s)**



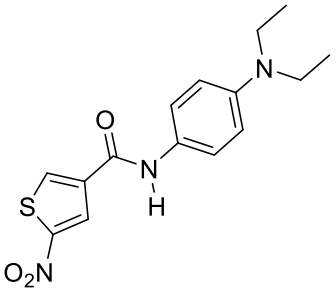
Synthesis according to the General procedure I. 4-Isothiazolecarboxylic acid (258 mg, 2.00 mmol), *N*,*N*-diethyl-*p*-phenylenediamine **17** (0.333 mL, 2.00 mmol), HBTU (986 mg, (2.60 mmol, 1.3 equiv), DIPEA (0.697 mL, 4.00 mmol, 2 equiv), DMF (5 mL). Solvent for extraction: diethyl ether. Recrystallization (MeOH/H_2O 10+1) without chromatography on silica gel gave compound **47s** (449 mg, 1.29 mmol, 64%) as brown crystals. M.p. 112.7–115.0 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.95 (s, 1H), 9.23 (d, 1H, J = 2.0 Hz), 8.40 (d, 1H, J = 2.0 Hz), 7.59 (m_c, 2H), 6.64 (m_c, 2H), 3.31 (q, 4H, J = 7.0 Hz), 1.07 (t, 6H, J = 7.0 Hz) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 159.3, 154.7, 151.1, 144.4, 127.0, 124.3, 122.0, 111.7, 43.7, 12.4 ppm. HRMS calc. for $C_{14}H_{18}N_3OS$ $[M+H]^+$: 276.1171, found 276.1183.

_N_-[4-(Diethylamino)phenyl]-5-methyl-4-phenylthiophene-3-carboxamide (47t)



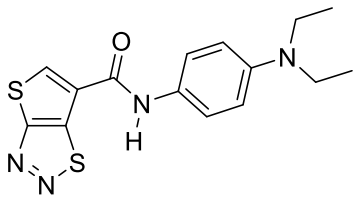
Synthesis according to the General procedure I. 5-Methyl-4-phenyl-thiophene-3-carboxylic acid, **46t**, (0.100 g, 0.458 mmol), *N*,*N*-diethyl-*p*-phenylenediamine **17** (76.2 μL, 0.458 mmol), HBTU (226 mg, 0.595 mmol, 1.3 equiv), DIPEA (0.160 mL, 0.916 mmol, 2 equiv), DMF (2 mL). Solvent for extraction: diethyl ether. Recrystallization (MeOH/H_2O 10+1) without chromatography on silica gel gave compound **47t** (99.0 mg, 0.272 mmol, 59%) as brown crystals. M.p. 118.8–119.6 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.65 (s, 1H), 7.73 (s, 1H), 7.42–7.24 (m, 7H), 6.57 (m_c, 2H), 3.26 (q, 4H, ^3J = 7.0 Hz), 2.32 (s, 3H), 1.04 (t, 6H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 162.2, 144.1, 139.1, 137.4, 135.4, 135.4, 135.3, 129.3, 127.9, 127.8, 126.8, 123.6, 121.4, 111.8, 43.7, 13.6, 12.3 ppm. HRMS calc. for $C_{22}H_{25}N_2OS$ $[M+H]^+$: 365.1688, found 365.1692.

_N_-[4-(Diethylamino)phenyl]-5-nitrothiophene-3-carboxamide (47u)



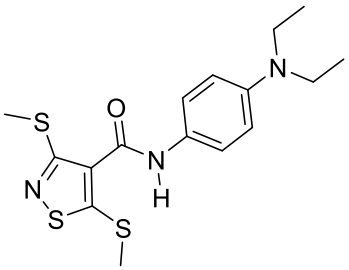
Synthesis according to the General procedure I. 5-Nitrothiophene-3-carboxylic acid **46u** (23.2 mg, 0.134 mmol), *N*,*N*-diethyl-*p*-phenylenediamine **17** (22.3 μL, 0.134 mmol), HBTU (66.1 mg, 0.174 mmol, 1.3 equiv), DIPEA (46.7 μL, 0.268 mmol, 2 equiv), DMF (1 mL). Solvent for extraction: diethyl ether. Chromatography on silica gel gave compound **47u** (35.3 mg, 0.111 mmol, 82%) as an orange solid. M.p. 197.9–200.1 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.01 (s, 1H), 8.64 (d, 1H, J = 1.9 Hz), 8.61 (d, 1H, J = 1.9 Hz), 7.49 (m_c, 2H), 6.66 (m_c, 2H), 3.31 (q, 4H, J = 7.0 Hz), 1.08 (t, 6H, J = 7.0 Hz) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 158.2, 151.1, 144.5, 136.8, 136.8, 128.0, 126.8, 122.2, 111.6, 43.7, 12.4 ppm. HRMS calc. for $C_{15}H_{18}N_3O_3S$ $[M+H]^+$: 320.1069, found 320.1071.

_N_-[4-(Diethylamino)phenyl]thieno[2,3-*d*][1,2,3]thiadiazole-6-carboxamide (47v)



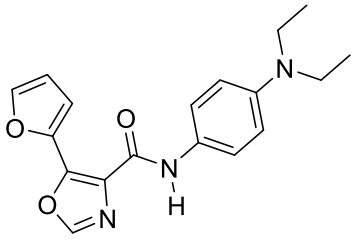
Synthesis according to the General procedure I. Deviating from the General procedure I, the reaction time was 3 d. Thieno[2,3-*d*][1,2,3]thiadiazole-6-carboxylic acid **46v** (25.0 mg, 0.134 mmol), *N*,*N*-diethyl-*p*-phenylenediamine **17** (22.3 μL, 0.134 mmol), HBTU (66.1 mg, 0.174 mmol, 1.3 equiv), DIPEA (46.7 μL, 0.268 mmol, 2 equiv), DMF (1 mL). Solvent for extraction: diethyl ether. Chromatography on silica gel gave compound **47v** (34.9 mg, 0.105 mmol, 78%) as a beige solid. M.p. 188.4–194.8 °C (decomp.). ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.35 (s, 1H), 9.12 (s, 1H), 7.51 (m_c, 2H), 6.68 (m_c, 2H), 3.32 (q, 4H, ^3J = 7.1 Hz), 1.09 (t, 6H, ^3J = 7.1 Hz) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.8, 157.6, 146.7, 144.6, 137.60, 126.9, 126.6, 122.2, 111.6, 43.7, 12.3 ppm. HRMS calc. for $C_{15}H_{17}N_4OS_2$ $[M+H]^+$: 332.0766, found 332.4437.

_N_-[4-(Diethylamino)phenyl]-3,5-bis(methylthio)isothiazole-4-carboxamide (47w)



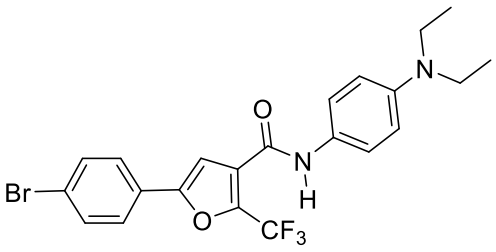
Synthesis according to the General procedure I. 3,5-Bis(methylthio)isothiazole-4-carboxylic acid **46w** (24.8 mg, 0.112 mmol), *N*,*N*-diethyl-*p*-phenylenediamine **17** (18.6 μL, 0.112 mmol), HBTU (55.2 mg, 0.146 mmol, 1.3 equiv), DIPEA (39.0, μL 0.224 mmol, 2 equiv), DMF (1 mL). Solvent for extraction: diethyl ether. Chromatography on silica gel gave compound **47w** (26.2 mg, 0.713 mmol, 64%) as a white solid. M.p. 138.9–142.2 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.88 (s, 1H), 7.42 (m$_c$, 2H), 6.65 (m$_c$, 2H), 3.31 (q, 4H, ^{3}J = 7.0 Hz), 2.63, 2.59 (each s, each 3H), 1.07 (t, 6H, ^{3}J = 7.0 Hz) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 165.4, 162.6, 159.0, 144.5, 128.9, 127.2, 121.3, 111.8, 43.7, 17.3, 13.5, 12.3 ppm. HRMS calc. for $C_{16}H_{22}N_3OS_3$ $[M+H]^+$: 368.0925, found 368.0930.

_N_-[4-(Diethylamino)phenyl]-5-(furan-2-yl)oxazole-4-carboxamide (47x)



Synthesis according to the General procedure I. 5-(Furan-2-yl)oxazole-4-carboxylic acid **46x** (35.1 mg, 0.196 mmol), *N*,*N*-diethyl-*p*-phenylenediamine **17** (32.6 μL, 0.196 mmol), HBTU (96.6 mg, 0.255 mmol, 1.3 equiv), DIPEA (68.3 μL, 0.392 mmol, 2 equiv), DMF (1.5 mL). Solvent for extraction: a mixture of ethyl acetate and diethyl ether (2:1) and water. Chromatography on silica gel gave compound **47x** (57.1 mg, 0.175 mmol, 90%) as a white solid. M.p. 88.2–90.5 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.79 (s, 1H), 8.61 (s, 1H), 7.94 (dd, 1H, ^{4}J = 0.8 Hz, ^{3}J = 1.8 Hz), 7.72 (dd, 1H, ^{3}J = 3.5 Hz, ^{4}J = 0.8 Hz), 7.57 (m$_c$, 2H), 6.73 (dd, 1H, ^{3}J = 3.5 Hz, ^{3}J = 1.8 Hz), 6.64 (m$_c$, 2H), 3.31 (q, 4H, ^{3}J = 7.0 Hz), 1.08 (t, 6H, ^{3}J = 7.0 Hz) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 158.0, 149.8, 145.0, 144.4, 143.5, 141.8, 127.9, 126.8, 122.2, 114.5, 112.3, 111.6, 43.7, 12.4 ppm. HRMS calc. for $C_{18}H_{20}N_3O_3$ $[M+H]^+$: 326.1505, found 326.1514.

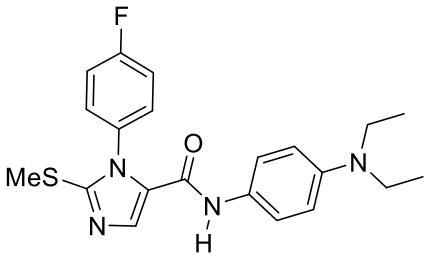
5-(4-Bromophenyl)-_N_-[4-(diethylamino)phenyl]-2-(trifluoromethyl)furan-3-carboxamide (47y)



Synthesis according to the General procedure I. 5-(4-Bromophenyl)-2-(trifluoromethyl)furan-3-carboxylic acid **46** (33.7 mg, 0.101 mmol), *N*,*N*-diethyl-*p*-phenylenediamine **17** (16.7 μL, 0.101 mmol), HBTU (47.8 mg, 0.131 mmol, 1.3 equiv), DIPEA (35.2 μL, 0.202 mmol, 2 equiv), DMF (1 mL). Solvent for extraction: diethyl ether and water/brine (2:1). Chromatography on silica gel gave compound **47y** (41.4 mg, 0.0860 mmol, 85%) as a yellow solid. M.p. 132.2–135.2 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.15 (s, 1H), 7.75 (m$_c$, 4H), 7.61 (q≈d, 1H, ^{5}J = 1.0 Hz), 7.46 (m$_c$, 2H), 6.66 (m$_c$, 2H), 3.31 (q, 4H, ^{3}J = 7.0 Hz), 1.08 (t, 6H, ^{3}J = 7.0 Hz) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 157.5, 153.3, 144.6, 137.5 (q, J = 41.8 Hz), 132.2, 127.2, 127.0 (q, J = 2.5 Hz), 126.8, 126.2, 122.7,

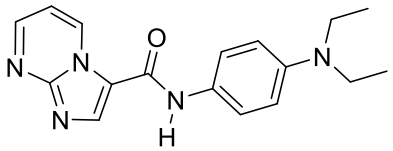
121.7, 118.8 (q, J = 268.2 Hz), 111.7, 107.5, 43.7, 12.3 ppm. HRMS calc. for $C_{22}H_{21}BrF_3N_2O_2$ $[M+H]^+$: 481.0739, found 481.0740.

N-[4-(Diethylamino)phenyl]-1-(4-fluorophenyl)-2-(methylthio)-1*H*-imidazole-5-carboxamide (47z)



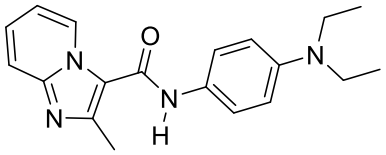
Synthesis according to the General procedure I. 1-(4-Fluorophenyl)-2-(methylthio)-1*H*-imidazole-5-carboxylic acid (91.0 mg, 0.361 mmol), *N*,*N*-diethyl-*p*-phenylenediamine **17** (60.0 μL, 1 equiv), HBTU (178 mg, 0.469 mmol, 1.3 equiv), DIPEA (0.126 mL, 0.722 mmol, 2 equiv), DMF (2 mL). Solvent for extraction: diethyl ether. Recrystallization (MeOH/H_2O 10+1) without chromatography on silica gel gave compound **47z** (133 mg, 0.333 mmol, 92%) as white needles. M.p. 197.0–198.7 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.73 (s, 1H), 7.86 (s, 1H), 7.40–7.27 (m, 6H), 6.58 (m_c, 2H), 3.27 (q, 4H, ^3J = 7.0 Hz), 2.54 (s, 3H, S), 1.04 (t, 6H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.8 (d, J = 245.8 Hz), 156.3, 148.5, 144.1, 132.6 (d, J = 3.4 Hz), 132.2, 129.6, 129.5 (d, J = 9.2 Hz), 127.2, 121.9, 115.7 (d, J = 22.8 Hz), 111.7, 43.7, 14.3, 12.3 ppm. HRMS calc. for $C_{21}H_{24}FN_4OS$ $[M+H]^+$: 399.1655, found 399.1657.

N-[4-(Diethylamino)phenyl]imidazo[1,2-*a*]pyrimidine-3-carboxamide (47aa)



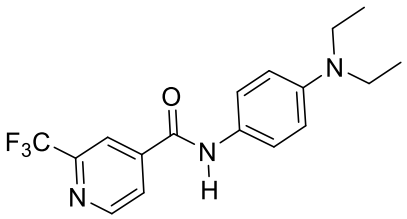
Synthesis according to the General procedure I. Imidazo[1,2-*a*]pyrimidine-3-carboxylic acid **46aa** (79.1 mg, 0.485 mmol), *N*,*N*-diethyl-*p*-phenylenediamine **17** (86.6 μL, 0.485 mmol), HBTU (239 mg, 0.631 mmol, 1.3 equiv), DIPEA (0.169 mL, 0.970 mmol, 2 equiv), DMF (2 mL). Solvent for extraction: ethyl acetate. Recrystallization (MeOH/H_2O 10+1) without chromatography on silica gel gave compound **47aa** (98.0 mg, 0.317 mmol, 65%) as fine beige crystals. M.p. 238.5–241.3 °C (decomp.). ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.02 (s, 1H), 9.77 (dd, 1H, ^3J = 6.9 Hz, ^4J = 2.0 Hz), 8.72 (dd, 1H, ^3J = 4.2 Hz), 8.65 (s, 1H), 7.50 (m_c, 2H), 7.28 (dd, 1H), 7.68 (m_c, 2H), 3.32 (q, 4H, ^3J = 7.0 Hz), 1.09 (t, 6H, ^3J = 7.0 Hz) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 157.6, 151.9, 149.6, 144.4, 137.8, 135.9, 126.8, 122.3, 116.9, 111.7, 110.2, 43.7, 12.4 ppm. HRMS calc. for $C_{17}H_{20}N_5O$ $[M+H]^+$: 310.1668, found 310.1675.

_N_-[4-(Diethylamino)phenyl]-2-methylimidazo[1,2-_a_]pyridine-3-carboxamide (47ab)



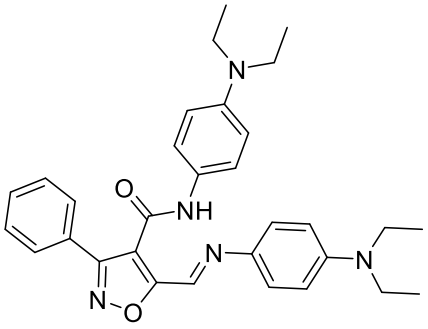
Synthesis according to the General procedure I. 2-Methylimidazo[1,2-*a*]pyridine-3-carboxylic acid **46ab** (0.100 g, 0.568 mmol), *N*,*N*-diethyl-*p*-phenylenediamine **17** (94.4 µL, 0.568 mmol), HBTU (0.280 g, 0.738 mmol, 1.3 equiv), DIPEA (0.198 mL, 1.14 mmol, 2 equiv), DMF (5 mL). Solvent for extraction: ethyl acetate. Automated chromatography on silica gel gave compound **47ab** (73.0 mg, 0.226 mmol, 40%) as greyish crystals. M.p. 176.3–177.3 °C (decomp.). ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.53 (s, 1H), 8.91 (ddd≈dt, 1H, ^{3}J = 6.9 Hz, ^{4}J = 1.2 Hz, ^{4}J = 1.2 Hz), 7.58 (ddd≈dt, 1H, ^{3}J = 9.0 Hz), 7.48 (m$_c$, 2H), 7.38 (ddd, 1H), 7.02 (ddd≈dt, 1H), 7.68 (m$_c$, 2H), 3.32 (q, 4H, ^{3}J = 7.0 Hz), 2.62 (s, 3H), 1.09 (t, 6H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 158.7, 145.1, 144.9, 144.4, 127.3, 126.9, 126.4, 122.0, 116.1, 112.8, 111.9, 43.7, 15.4, 12.3 ppm. HRMS calc. for $C_{19}H_{23}N_4O$ $[M+H]^+$: 323.1872, found 323.1876.

_N_-[4-(Diethylamino)phenyl]-2-(trifluoromethyl)isonicotinamide (47ac)



Synthesis according to the General procedure I. Deviating from the General procedure I, the reaction time was 3 d at room temperature. 2-(Trifluoromethyl)isonicotinic acid **46ac** (0.100 g, 0.523 mmol) *N*,*N*-diethyl-*p*-phenylenediamine **17** (87.0 µL, 0.523 mmol), HBTU (258 mg, 0.680 mmol, 1.3 equiv), DIPEA (0.182 mL, 1.05 mmol, 2 equiv), DMF (3 mL). Solvent for extraction: diethyl ether. Chromatography on silica gel gave compound **47ac** (163 mg, 0.483 mmol, 92%) as an orange resin. M.p. 107.4–108.9 °C (decomp.). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.37 (s, 1H), 8.96 (d, 1H, J = 5.0 Hz), 8.34 (bd, 1H), 8.18 (dd, 1H, J = 1.2 Hz), 7.54 (m$_c$, 2H), 6.68 (m$_c$, 2H), 3.32 (q, 4H, ^{3}J = 7.0 Hz), 1.09 (t, 6H, ^{3}J = 7.0 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.3, 150.9, 147.0 (q, J = 34.0 Hz), 144.8, 144.2, 126.7, 125.1, 122.3, 121.5 (q, J = 274.2 Hz), 118.2 (q, J = 2.8 Hz), 111.5, 43.7, 12.3 ppm. HRMS calc. for $C_{17}H_{19}F_3N_3O$ $[M+H]^+$: 338.1480, found 338.1481.

(_E_)-_N_-[4-(Diethylamino)phenyl]-5-[[(4-(diethylamino)phenyl]imino]methyl]-3-phenylisoxazole-4-carboxamide (48)

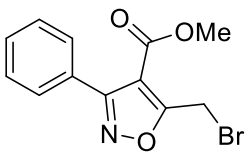


5-Methyl-3-phenylisoxazole-4-carboxylic acid (2.03 g, 10.0 mmol) was dissolved in carbon tetrachloride (40 mL) under argon. *N*-Bromosuccinimide (1.78 g, 10.0 mmol) and benzoylperoxide (242 mg, 1.00 mmol) were added, and the reaction mixture was heated under reflux conditions for 8.5 h at 60 °C, stirred at room temperature overnight and heated for 6 h at 60 °C. The solution was filtered after cooling to rt, washed once with water and the aqueous phase was extracted once with DCM. The combined organic phases were extracted with a 2 M solution of sodium hydroxide in H_2O. The aqueous phase was acidified with 1 M hydrochloric acid and extracted with ethyl acetate. The organic

phase was washed neutral with water (twice). The solvent was removed with a rotary evaporator and the crude product was subjected to automated chromatography. The chromatography on silica gel was performed with an increasing gradient of ethyl acetate in *n*-hexane, starting with 0% of ethyl acetate, but it was not able to separate the mixture of intermediates. The resulting crude product mixture (380 mg) was dissolved in absolute DMF (5 mL). *N*,*N*-Diethyl-*p*-phenylenediamine hydrochloride **50** (442 mg, 1.87 mmol), HBTU (1.42 g, 3.74 mmol) and DIPEA (1.63 mL, 9.35 mmol) were added to the solution, and the reaction mixture was stirred for 2 d at room temperature. The reaction mixture was diluted with ethyl acetate, and washed with a mixture of water and brine (50%). The phases were separated and the aqueous phase was extracted once with ethyl acetate. The combined organic phases were washed once with a small amount of water and the solvent was removed with a rotary evaporator. The crude product was subjected to automated chromatography. Recrystallization (MeOH/H_2O 10+1) after automated chromatography on silica gel, using an increasing gradient of ethyl acetate in *n*-hexane, starting with 0% of ethyl acetate, gave compound **48** (129 mg, 0.253 mmol, 3%) as fine orange needles M.p. 175.3–177.0 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.63 (s, 1H), 8.70 (s, 1H), 7.80–7.74 (m, 2H), 7.59–7.49 (m, 3H), 7.43, 7.38 (each m$_c$, each 2H), 6.71, 6.65 (each m$_c$, each 2H), 3.39, 3.31 (each q, each 4H, each ^3J = 7.0 Hz), 1.10, 1.07 (each t, each 6H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 165.0, 161.0, 158.0, 148.1, 144.6, 138.0, 136.3, 130.3, 128.9, 128.9, 127.9, 127.1, 124.1, 121.8, 115.9, 111.7, 111.5, 43.9, 43.8, 12.5, 12.4 ppm. HRMS calc. for $C_{31}H_{35}N_5O_2$ $[M+2H]^{2+}$: 255.6474, found 255.6479.

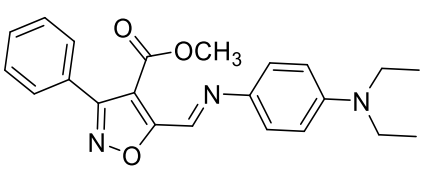
Methyl (*E*)-5-[[[4-(diethylamino)phenyl]imino]methyl]-3-phenylisoxazole-4-carboxylate (51)

i. Methyl 5-(bromomethyl)-3-phenylisoxazole-4-carboxylate (**53**)



Methyl 5-methyl-3-phenylisoxazole-4-carboxylate (2.17 g, 10.0 mmol) was dissolved in carbon tetrachloride (40 mL) under argon. *N*-Bromosuccinimide (1.78 g, 10.0 mmol) and benzoylperoxide (242 mg, 1.00 mmol, 0.1 equiv) were added, and the reaction mixture was heated under reflux conditions for 6 h to 60 °C and stirred at room temperature for 4 d. The solution was dissolved to ethyl acetate and extracted three times with H_2O. The solvent was removed with a rotary evaporator, and the crude product was subjected to automated chromatography. The chromatography on silica gel, with an increasing gradient of ethyl acetate in *n*-hexane, starting with 0% of ethyl acetate gave compound **53**, which was used in a next step without further purification.

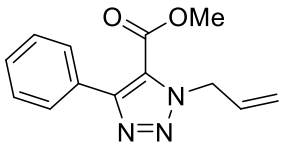
ii. Methyl (E)-5-[[[4-(diethylamino)phenyl]imino]methyl]-3-phenylisoxazole-4-carboxylate (**51**)



Crude mixture of methyl 5-(bromomethyl)-3-phenylisoxazole-4-carboxylate **53** (135 mg, purity ~50%) was dissolved in methanol (2 mL) and *N*,*N*-diethyl-*p*-phenylenediamine **17** (0.0758 mL, 0.456 mmol) was added to the solution. The reaction mixture was irradiated in a microwave (30 min, 120 °C). Diethyl ether was added, and organic phase was washed twice with a 0.5 M solution of NaOH in H_2O and two times with H_2O and brine. Recrystallization (EtOH/H_2O) without chromatography gave compound **51** (61 mg, 0.16 mmol, 2%) as red needles. M.p. 109.7–111.0 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.91

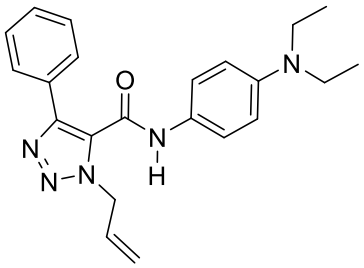
(s, 1H), 7.71–7.65 (m, 2H), 7.59–7.49 (m, 3H), 7.45 (m_c, 2H), 6.76 (m_c, 2H), 3.80 (s, 3H), 3.42 (q, 4H, ^3J = 7.0 Hz), 1.13 (t, 6H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 169.0, 162.2, 161.2, 148.5, 137.8, 136.4, 130.2, 129.1, 128.3, 127.5, 124.5, 111.5, 110.6, 52.3, 44.0, 12.5 ppm. HRMS calc. for $C_{22}H_{24}N_3O_3$ $[M+H]^+$: 378.1818, found 378.1823.

Methyl 1-allyl-4-phenyl-1*H*-1,2,3-triazole-5-carboxylate (SI55)



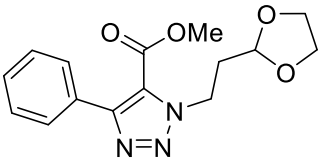
Synthesis according to the General procedure VIII, Method A. Methyl phenylpropiolate (0.160 g, 1.00 mmol), allyl bromide (86.5 μL, 1.00 mmol), TBAB (322 mg, 1.00 mmol), sodium azide (65.0 mg, 1.00 mmol), solvent volume: 1.5 mL each. Reaction conditions: 150 °C for 70 min. Solvent for extraction: once with ethyl acetate and once with toluene. Chromatography on silica gel gave compound **SI55** (21.2 mg, 0.0871 mmol, 9%) as a brownish oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.76–7.69 (m, 2H), 7.48–7.39 (m, 3H), 6.07 (m_c, 1H), 5.38–5.21 (m, 4H), 3.85 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.8, 150.5, 131.8, 130.4, 129.4, 129.1, 128.2, 124.0, 119.4, 53.3, 52.5 ppm. HRMS calc. for $C_{13}H_{14}N_3O_2$ $[M+H]^+$: 244.1086, found 244.1092.

1-Allyl-*N*-[4-(diethylamino)phenyl]-4-phenyl-1*H*-1,2,3-triazole-5-carboxamide (SI56)



Synthesis according to the General procedure VI. Deviating from the General procedure VI, both reaction times were 2 d at room temperature. Methyl 1-allyl-5-phenyl-1*H*-1,2,3-triazole-4-carboxylate **SI55** (19.8 mg, 0.0814 mmol), $LiOH{\cdot}H_2O$ (5.10 mg, 0.122 mmol, 1.5 equiv), solvent volume: 200 μL each. *N*,*N*-Diethyl-*p*-phenylenediamine (13.5 μL, 0.0814 mmol), HBTU (40.1 mg, 0.106 mmol, 1.3 equiv), DIPEA (28.4 μL, 0.163 mmol, 2 equiv), DMF (1 mL). Solvent for extraction: ethyl acetate. Chromatography on silica gel gave compound **SI56** (21.9 mg, 0.0583 mmol, 72%) as a colorless oil. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.52 (s, 1H), 7.80–7.75 (m, 2H), 7.50–7.34 (m, 5H), 6.66 (m_c, 2H), 6.04 (m, 1H), 5.29–5.09 (m, 2H), 3.32 (q, 4H, ^3J = 7.0 Hz), 1.08 (t, 6H, ^3J = 7.0 Hz) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 156.7, 144.9, 143.5, 131.8, 130.1, 130.0, 128.8, 128.3, 126.3, 126.3, 121.7, 119.0, 111.6, 51.2, 43.7, 12.3 ppm. HRMS calc. for $C_{22}H_{26}N_5O$ $[M+H]^+$: 376.2137, found 376.2136.

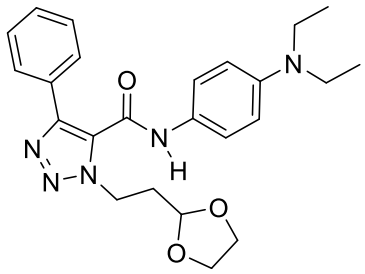
Methyl 1-[2-(1,3-dioxolan-2-yl)ethyl]-4-phenyl-1*H*-1,2,3-triazole-5-carboxylate (SI57)



Synthesis according to the General procedure VIII, Method A. Methyl phenylpropiolate (0.160 g, 1.00 mmol), 2-(2-bromoethyl)-1,3-dioxolane (0.120 mL, 1.00 mmol), TBAB (322 mg, 1.00 mmol), sodium azide (65.0 mg, 1.00 mmol), solvent volume: 1.5 mL each. reaction conditions: stirring overnight at room temperature and 70 min in the microwave

reactor at 150 °C. Solvent for extraction: twice with toluene and once with ethyl acetate. Chromatography on silica gel gave compound **SI57** (33.5 mg, 0.110 mmol, 11%) as a brownish oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.89–7.80 (m, 2H), 7.49–7.37 (m, 3H), 5.03 (t, 1H, ^{3}J = 4.3 Hz), 4.61 (m_c, 2H), 4.03–3.81 (m, 7H), 2.44 (m_c, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.9, 150.1, 135.5, 129.8, 129.6, 129.3, 128.3, 101.8, 65.3, 52.4, 51.0, 33.6 ppm. HRMS calc. for $C_{15}H_{18}N_3O_4$ $[M+H]^+$: 304.1297, found 304.1298.

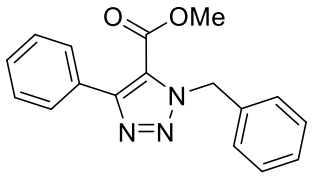
1-[2-(1,3-Dioxolan-2-yl)ethyl]-*N*-[4-(diethylamino)phenyl]-4-phenyl-1*H*-1,2,3-triazole-5-carboxamide (SI58)



Synthesis according to the General procedure VI. Deviating from the General procedure VI, the reaction time of the hydrolysis was 2 d at room temperature. Methyl 1-[2-(1,3-dioxolan-2-yl)ethyl]-4-phenyl-1*H*-1,2,3-triazole-5-carboxylate **SI57** (37.8 mg, 0.125 mmol), $LiOH{\cdot}H_2O$ (7.80 mg, 0.187 mmol, 1.5 equiv), solvent volume: 200 µL each. *N*,*N*-Diethyl-*p*-phenylenediamine **17** (20.8 µL, 0.125 mmol), HBTU (61.6 mg, 0.163 mmol, 1.3 equiv), DIPEA (43.5 µL, 0.250 mmol, 2 equiv), DMF (1 mL). Solvent for extraction: ethyl acetate. Chromatography on silica gel gave compound **SI58** (34.7 mg, 0.0797 mmol, 64%) as a brown oil. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.08 (s, 1H), 7.92–7.86 (m, 2H), 7.51 (m_c, 2H), 7.49–7.37 (m, 3H), 6.65 (m_c, 2H), 4.99 (t, 1H, ^{3}J = 4.5 Hz), 4.61 (dd≈t, 2H, ^{3}J = 7.3 Hz, ^{3}J = 7.3 Hz), 3.99–3.76 (m, 4H), 3.31 (q, 4H, ^{3}J = 7.0 Hz), 2.33 (m_c, 2H), 1.08 (t, 6H, ^{3}J = 7.0 Hz) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 158.7, 145.7, 144.4, 139.4, 129.6, 128.6, 128.2, 128.0, 127.0, 122.0, 111.7, 101.0, 64.4, 50.2, 43.7, 33.1, 12.3 ppm. HRMS calc. for $C_{24}H_{30}N_5O_3$ $[M+H]^+$: 436.2349, found 436.2351.

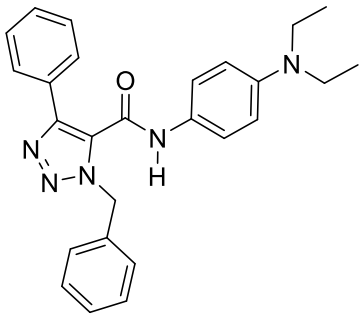
1-Benzyl-*N*-[4-(diethylamino)phenyl]-4-phenyl-1*H*-1,2,3-triazole-5-carboxamide (SI60)

i. Methyl 1-benzyl-4-phenyl-1H-1,2,3-triazole-5-carboxylate (**SI59**)



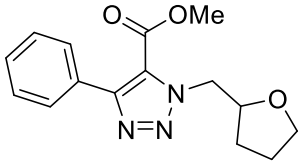
Synthesis according to the General procedure VIII, method A. Methyl phenylpropiolate (80.1 mg, 0.500 mmol), benzyl bromide (59.5 µL, 0.500 mmol), TBAB (161 mg, 0.500 mmol), sodium azide (32.5 mg, 0.500 mmol). solvent volume: 1 mL each. Reaction conditions: 20 min, 130 °C and 70 min, 150 °C. Solvent for extraction: twice with toluene. Chromatography on silica gel gave compound **SI59** (34.1 mg, 0.116 mmol, 23%) as a colorless resin. HRMS calc. for $C_{17}H_{16}N_3O_2$ $[M+H]^+$: 294.1243, found 294.1246.

ii. 1-Benzyl-N-[4-(diethylamino)phenyl]-4-phenyl-1H-1,2,3-triazole-5-carboxamide (**SI60**)



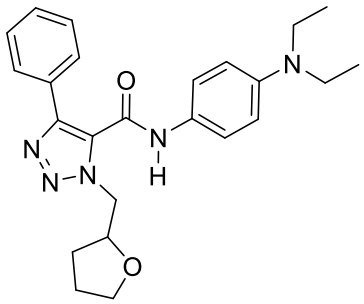
Synthesis according to the General procedure VI. Deviating from the General procedure VI, the reaction time of the amide coupling was 2 d at room temperature. Methyl 1-benzyl-4-phenyl-1*H*-1,2,3-triazole-5-carboxylate **SI59** (20.3 mg, 0.0692 mmol), LiOH·H_2O (4.40 mg, 0.104 mmol, 1.5 equiv), Solvent volume: 200 µL each. *N*,*N*-Diethyl-*p*-phenylenediamine **17** (11.5 µL, 0.0692 mmol), HBTU (34.1 mg, 0.0900 mmol, 1.3 equiv), DIPEA (24.1 µL, 0.138 mmol, 2 equiv), DMF (1 mL). Solvent for extraction: diethyl ether. Chromatography on silica gel gave compound **SI60** (19.3 mg, 0.0454 mmol, 66%) as yellow needles. M.p. 173.9–175.5 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.52 (s, 1H), 7.78–7.74 (m, 2H), 7.49–7.27 (m, 10H), 6.64 (m_c, 2H), 5.69 (s, 2H), 3.31 (q, 4H, ^3J = 7.0 Hz), 1.08 (t, 6H, ^3J = 7.0 Hz) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 156.7, 144.9, 143.6, 135.1, 130.0, 129.9, 128.7, 128.6, 128.3, 128.1, 127.9, 126.3, 126.2, 121.8, 111.6, 52.2, 43.7, 12.3 ppm. HRMS calc. for $C_{26}H_{28}N_5O$ $[M+H]^+$: 426.2294, found 426.2299.

Methyl 4-phenyl-1-[(tetrahydrofuran-2-yl)methyl]-1*H*-1,2,3-triazole-5-carboxylate (SI61)



Synthesis according to the General procedure VIII, method B. Methyl phenylpropiolate (0.160 g, 1.00 mmol), 2-(chloromethyl)tetrahydrofuran (0.109 mL, 1.00 mmol), sodium azide (65.0 mg, 1.00 mmol). Solvent volume: 2 mL. Reaction conditions: first 60 min, 80 °C, then 50 min, 140 °C. Chromatography on silica gel gave compound **SI61** (49.6 mg, 0.173 mmol, 17%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.89–7.81 (m, 2H), 7.48–7.38 (m, 3H), 4.65–4.46 (m, 3H), 3.96–3.76 (m, 5H), 2.14-1.72 (m, 4H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.8, 150.3, 135.7, 129.6, 129.4, 129.3, 128.3, 77.1, 68.7, 59.6, 52.4, 29.3, 25.6 ppm. HRMS calc. for $C_{15}H_{18}N_3O_3$ $[M+H]^+$: 288.1348, found 288.1350.

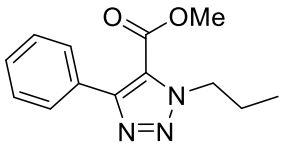
***N*-[4-(Diethylamino)phenyl]-4-phenyl-1-[(tetrahydrofuran-2-yl)methyl]-1*H*-1,2,3-triazole-5-carboxamide (SI62)**



Synthesis according to the General procedure VI. Methyl 4-phenyl-1-[(tetrahydrofuran-2-yl)methyl]-1*H*-1,2,3-triazole-5-carboxylate **SI61** (34.7 mg, 0.121 mmol), LiOH·H_2O (7.60 mg, 0.181 mmol, 1.5 equiv). Solvent volume: 0.200 mL each. *N*,*N*-Diethyl-*p*-phenylenediamine **17** (20.1 µL, 0.121 mmol), HBTU (59.7 mg, 0.157 mmol, 1.3 equiv), DIPEA (42.2 µL, 0.242 mmol, 2 equiv), DMF (1 mL). Solvent for extraction: diethyl ether. Chromatography on silica gel gave compound **SI62** (34.1 mg, 0.0813 mmol, 67%) as a brownish oil. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.10 (s, 1H), 7.90–7.85 (m, 2H), 7.51 (m_c, 2H), 7.49–7.37 (m, 3H), 6.65 (m_c, 2H), 4.63–4.40 (m, 3H), 3.79 (m_c, 1H), 3.67 (m_c, 1H), 3.31 (q, 4H, ^3J = 7.0 Hz), 1.21–1.69 (m, 4H), 1.08 (t, 6H, ^3J = 7.0

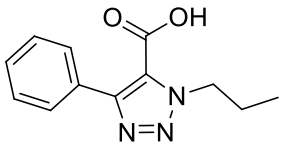
Hz) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 158.7, 145.7, 144.4, 139.5, 129.6, 128.6, 128.3, 128.0, 127.0, 122.0, 111.7, 76.5, 67.4, 58.5, 43.7, 28.4, 24.9, 12.3 ppm. HRMS calc. for $C_{24}H_{30}N_5O_2$ $[M+H]^+$: 420.2400, found 420.2397.

Methyl 4-phenyl-1-propyl-1*H*-1,2,3-triazole-5-carboxylate (SI63)



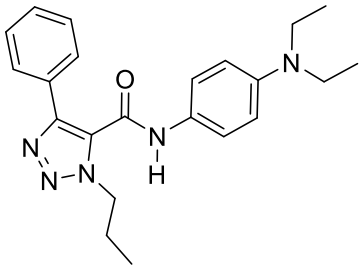
Synthesis according to the General procedure VIII, method B. Methyl phenylpropiolate (0.160 g, 1.00 mmol), propyl bromide (90.8 μL, 1.00 mmol), sodium azide (65.0 mg, 1.00 mmol). solvent volume: 2.5 mL. reaction conditions: first 60 min, 70 °C, then 70 min, 140 °C. Chromatography on silica gel gave compound **SI63** (118 mg, 0.481 mmol, 48%) as a brownish oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.89–7.81 (m, 2H), 7.49–7.38 (m, 3H), 4.47 (t, 2H, ^3J = 7.1 Hz), 3.93 (s, 3H), 2.07 (tq≈sext, 2H, ^3J = 7.1 Hz, ^3J = 7.4 Hz), 0.99 (t, 3H, ^3J = 7.4 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.9, 150.1, 135.3, 129.7, 129.3, 128.3, 57.6, 52.4, 23.3, 11.2 ppm. HRMS calc. for $C_{13}H_{16}N_3O_2$ $[M+H]^+$: 246.1243, found 246.1247.

4-Phenyl-1-propyl-1*H*-1,2,3-triazole-5-carboxylic acid (SI64)



A mixture of methyl 4-phenyl-1-propyl-1*H*-1,2,3-triazole-5-carboxylate **SI63** (83.4 mg, 0.340 mmol) and lithum hydroxide monohydrate (21.4 mg, 0.510 mmol, 1.5 equiv) in an equimixture of THF, methanol and water (0.90 mL) was stirred overnight at room temperature. The reaction mixture was diluted with ethyl acetate and transferred to a separatory funnel. Water was added and the mixture was acidified with 1 M hydrochloric acid. The phases were separated, the organic phase was washed neutral with three portions of water, and the organic solvent was removed with a rotary evaporator to give compound **SI64** (79.0 mg, 0.342 mmol, quant.) as a slightly white solid. M.p. 102.9–106.4 °C. ^{1}H NMR (300 MHz, Acetone-d_6): δ 11.47 (br s, 1H), 7.96–7.88 (m, 2H), 7.49–7.37 (m, 3H), 4.49 (t, 2H, ^3J = 7.0 Hz), 2.05 (m_c, 2H), 0.98 (t, 3H, ^3J = 7.4 Hz) ppm.

***N*-[4-(Diethylamino)phenyl]-4-phenyl-1-propyl-1*H*-1,2,3-triazole-5-carboxamide (SI65)**

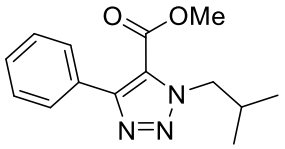


Synthesis according to the General procedure I. 4-Phenyl-1-propyl-1*H*-1,2,3-triazole-5-carboxylic acid **SI64** (28.0 mg, 0.121 mmol), *N*,*N*-diethyl-*p*-phenylenediamine **17** (20.1 μL, 0.121 mmol), HBTU (59.7 mg, 0.157 mmol, 1.3 equiv), DIPEA (42.2 μL, 0.242 mmol, 2 equiv), DMF (1.5 mL). Solvent for extraction: diethyl ether. Chromatography on silica gel gave compound **SI65** (31.7 mg, 0.0840 mmol, 69%) as a brownish resin. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.09 (s, 1H), 7.91–7.85 (m, 2H), 7.51 (m_c, 2H), 7.49–7.36 (m, 3H), 6.64 (m_c, 2H), 4.49 (t, 2H, ^3J = 7.0 Hz), 3.31 (q, 4H, ^3J = 7.0 Hz), 2.00 (tq≈sext, ^3J = 7.0 Hz, ^3J = 7.5 Hz, 2H), 1.08 (t, 6H, ^3J = 7.0 Hz), 0.95 (t, 3H, ^3J =

7.5 Hz) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 158.8, 145.6, 144.4, 139.3, 129.7, 128.6, 128.3, 128.0, 127.0, 122.0, 111.7, 56.3, 43.7, 22.5, 12.3, 10.9 ppm. HRMS calc. for $C_{22}H_{28}N_5O$ $[M+H]^+$: 378.2294, found 378.2293.

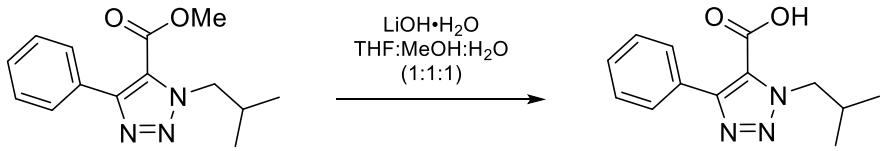
N-[4-(Diethylamino)phenyl]-1-isobutyl-4-phenyl-1*H*-1,2,3-triazole-5-carboxamide (SI68)

i. Methyl 1-isobutyl-4-phenyl-1H-1,2,3-triazole-5-carboxylate (**SI66**)



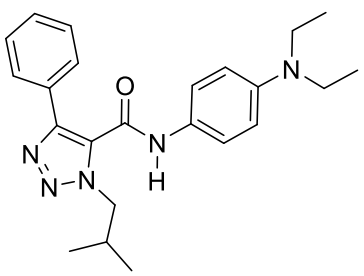
Synthesis according to the of the General procedure VIII, method B. Methyl phenylpropiolate (0.160 g, 1.00 mmol), 1-bromo-2-methylpropane (0.109 mL, 1.00 mmol), sodium azide (65.0 mg, 1.00 mmol). solvent volume: 2.5 mL. reaction conditions: first 60 min, 70 °C, then 70 min, 140 °C. Chromatography on silica gel gave compound **SI66** (174 mg, 0.671 mmol, 67%) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.90–7.81 (m, 2H), 7.49–7.38 (m, 3H), 4.32 (d, 2H, ^3J = 7.3 Hz), 3.93 (s, 3H), 2.45 (m_c, 2H), 0.98 (d, 6H, ^3J = 6.7 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.9, 150.1, 135.3, 129.7, 129.3, 129.3, 128.3, 63.0, 52.4, 29.6, 20.0 ppm. HRMS calc. for $C_{14}H_{18}N_3O_2$ $[M+H]^+$: 260.1399, found 260.1402.

ii. 1-Isobutyl-4-phenyl-1H-1,2,3-triazole-5-carboxylic acid (**SI67**)



SI66 **SI67**

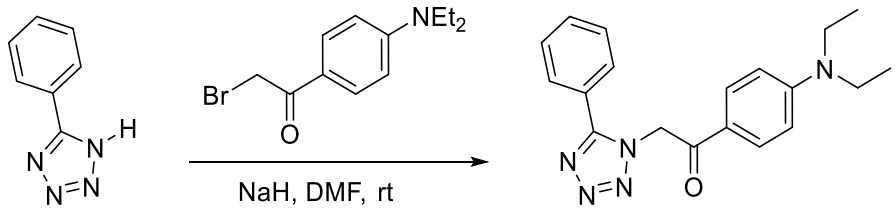
A mixture of methyl 1-isobutyl-4-phenyl-1*H*-1,2,3-triazole-5-carboxylate **SI66** (135 mg, 0.521 mmol) and lithum hydroxide monohydrate (32.8 mg, 0.781 mmol, 1.5 equiv) in an equimixture of THF, methanol and water (1.20 mL) was stirred overnight at room temperature. The reaction mixture was diluted with ethyl acetate and transferred to a separatory funnel. Water was added, and the mixture was acidified with 1 M hydrochloric acid. The phases were separated, the organic phase was washed neutral with three portions of water, and the solvent was removed with a rotary evaporator to give compound **SI67** (123 mg, 0.501 mmol, 96%) as a white solid that was used in the next step without further purification. M.p. 88.4–94.8 °C.



iii. N-[4-(Diethylamino)phenyl]-1-isobutyl-4-phenyl-1H-1,2,3-triazole-5-carboxamide (**SI68**): Synthesis according to the General procedure I. 1-Isobutyl-4-phenyl-1*H*-1,2,3-triazole-5-carboxylic acid **SI67** (36.8 mg, 0.150 mmol), *N*,*N*-diethyl-*p*-phenylenediamine **17** (24.9 μL, 1.50 mmol), HBTU (74.0 mg, 0.195 mmol, 1.3 equiv), DIPEA (52.3 μL, 0.300 mmol, 2 equiv), DMF (1.5 mL). Solvent for extraction: ethyl acetate. Chromatography on silica gel gave compound **SI68** (49.7 mg, 0.127 mmol, 85%) as a yellowish oil. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.06 (s, 1H), 7.91–7.86 (m, 2H), 7.50 (m_c, 2H), 7.49–7.37 (m, 3H), 6.65 (m_c, 2H), 4.35 (d, 2H, ^3J = 6.9 Hz),

3.31 (q, 4H, ^3J = 7.0 Hz), 2.35 (m_c, 1H), 1.08 (t, 6H, ^3J = 7.0 Hz), 0.96 (d, 3H, ^3J = 6.8 Hz) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 158.8, 145.5, 144.4, 139.3, 129.7, 128.6, 128.3, 128.0, 127.0, 122.0, 111.7, 61.6, 43.7, 28.9, 19.5, 12.3 ppm. HRMS calc. for $C_{23}H_{30}N_5O$ $[M+H]^+$: 392.2450, found 392.2454.

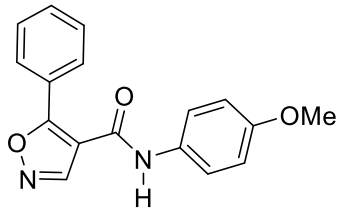
1-[4-(Diethylamino)phenyl]-2-(5-phenyl-1*H*-tetrazol-1-yl)ethanone (SI69)



SI69

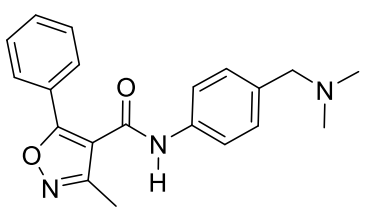
A mixture of 5-phenyl-1*H*-tetrazole (189 mg, 1.30 mmol) and a 60% suspension of sodium hydride in mineral oil (62.2 mg, 1.56 mmol, 1.2 equiv) in absolute DMF (2.5 mL) was stirred for 1.5 h at room temperature under argon. 2-Bromo-1-[4-(diethylamino)phenyl]ethanone (0.350 g, 1.30 mmol) was added, and the reaction mixture was stirred for 2 d at room temperature. The reaction mixture was diluted with ethyl acetate, washed three times with water and the organic solvent was removed with a rotary evaporator. The crude product was purified by automated chromatography on silica gel, using a gradient of increasing ethyl acetate starting with 100% *n*-hexane to give compound **SI69** (183 mg, 0.547 mmol, 42%) as an orange resin. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.21–8.13 (m, 2H), 7.86 (m_c, 2H), 7.51–7.42 (m, 3H), 6.67 (m_c, 2H), 6.01 (s, 3H), 3.45 (q, 4H, ^3J = 7.1 Hz), 1.24 (t, 6H, ^3J = 7.1 Hz) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 186.1, 165.6, 152.3, 131.0, 130.4, 128.9, 127.7, 127.2, 121.2, 110.7, 57.7, 44.8, 12.6 ppm. HRMS calc. for $C_{19}H_{22}N_5O$ $[M+H]^+$: 336.1824, found 336.1823.

***N*-(4-Methoxyphenyl)-5-phenylisoxazole-4-carboxamide (SI70)**



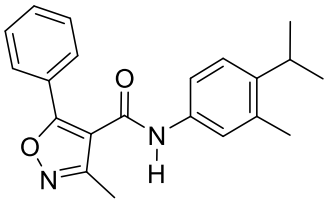
Synthesis according to the General procedure I. 5-Phenylisoxazole-4-carboxylic acid **46d** (189 mg, 1.00 mmol), 4-methoxyaniline (123 mg, 1.00 mmol), HBTU (493 mg, 1.30 mmol, 1.3 equiv), DIPEA (0.348 mL, 2.00 mmol, 2 equiv), DMF (3 mL). Solvent for extraction: diethyl ether. Recrystallization (MeOH/H_2O 19+1) gave compound **SI70** (125 mg, 0.425 mmol, 42%) as white needles. M.p. 129.7–133.0 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.30 (s, 1H), 9.09 (s, 1H), 8.01–7.94 (m, 2H), 7.63–7.51 (m, 5H), 6.93 (m_c, 2H), 3.74 (s, 3H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 167.9, 158.7, 155.8, 151.1, 131.6, 131.2, 128.9, 127.9, 126.3, 126.3, 121.7, 113.9, 112.7, 55.2 ppm. HRMS calc. for $C_{17}H_{15}N_2O_3$ $[M+H]^+$: 295.1083, found 295.1077.

_N_-[4-[(Dimethylamino)methyl]phenyl]-5-phenylisoxazole-4-carboxamide (SI71)



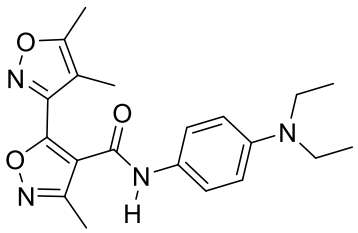
Synthesis according to the General procedure I. 3-Methyl-5-phenylisoxazole-4-carboxylic acid (61.4 mg, 0.302 mmol), 4-[(dimethylamino)methyl]aniline hydrochloride (56.4 mg, 0.302 mmol), HBTU (149 mg, 0.393 mmol, 1.3 equiv), DIPEA (0.158 mL, 0.906 mmol, 3 equiv), DMF (1.5 mL). Solvent for extraction: ethyl acetate and washing with an equimixture of water and brine, 4 times. Recrystallization after chromatography on silica gel gave compound **SI71** (73.3 mg, 0.219 mmol, 72%) as white needles. M.p. 128.3–130.0 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.50 (s, 1H), 7.85–7.77 (m, 2H), 7.59 (m$_c$, 2H), 7.58–7.51 (m, 3H), 7.26 (m$_c$, 2H), 3.35 (s, 2H), 2.36 (s, 3H), 2.14 (s, 6H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 166.0, 159.9, 158.9, 137.2, 134.8, 130.9, 129.2, 129.1, 126.6, 126.4, 119.5, 113.5, 62.9, 44.8, 10.2 ppm. HRMS calc. for $C_{20}H_{22}N_3O_2$ [M+H]$^+$: 336.1712, found 336.1717.

_N_-(4-Isopropyl-3-methylphenyl)-3-methyl-5-phenylisoxazole-4-carboxamide (SI72)



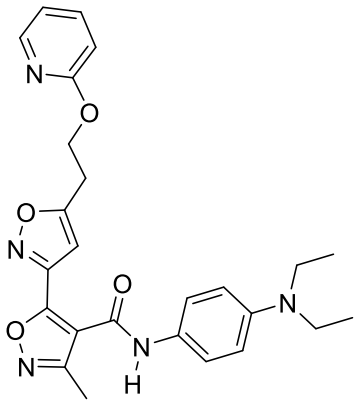
Synthesis according to the General procedure I. 3-Methyl-5-phenylisoxazole-4-carboxylic acid (40.0 mg, 0.197 mmol), 4-isopropyl-3-methylaniline hydrochloride (36.6 mg, 0.197 mmol), HBTU (97.1 mg, 0.256 mmol, 1.3 equiv), DIPEA (0.103 mL, 0.591 mmol, 2 equiv), DMF (1 mL). Solvent for extraction: diethyl ether/ethyl acetate (1:1). Recrystallization (EtOH/H_2O 10+1) without chromatographic purification gave compound **SI72** (55.1 mg, 0.165 mmol, 84%) as fine white needles. M.p. 165.1–166.6 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.38 (s, 1H), 7.85–7.76 (m, 2H), 7.59–7.50 (m, 3H), 7.46–7.38 (m, 2H), 7.20 (bd, 1H, ^{3}J = 8.9 Hz), 3.07 (sep, 1H, ^{3}J = 6.8 Hz), 2.35 (s, 3H), 2.28 (s, 3H), 1.17 (d, 6H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 165.8, 159.8, 158.9, 142.3, 135.8, 134.9, 130.8, 129.1, 126.5, 126.4, 124.9, 121.3, 117.8, 113.5, 28.3, 23.1, 10.1 ppm. HRMS calc. for $C_{21}H_{23}N_2O_2$ [M+H]$^+$: 335.1760, found 335.1765.

_N_-[4-(Diethylamino)phenyl]-3',4,5-trimethyl-[3,5'-biisoxazole]-4'-carboxamide (SI73)



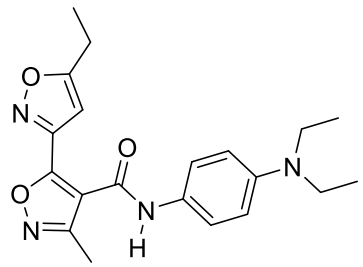
Synthesis according to the General procedure I. 3',4,5-trimethyl-[3,5'-biisoxazole]-4'-carboxylic acid (0.020 g, 0.090 mmol), *N*,*N*-diethyl-*p*-phenylenediamine **17** (22 µL, 0.140 mmol, 1.5 equiv), HBTU (80.9 mg, 0.213 mmol, 1.3 equiv), DIPEA (31 µL, 0.180 mmol, 2.0 equiv), DMF (2 mL). Solvent for extraction: diethyl ether. Eluent for purification: *n*-heptane/EtOAc 4:1. Chromatography on silica gel gave compound **SI73** (35.5 mg, 0.0104 mmol, 88%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.62 (s, 1H), 7.50 (m$_c$, 2H), 6.67 (m$_c$, 2H), 3.34 (q, ^{3}J = 7.1 Hz, 4H), 2.66 (s, 3H), 2.47 (d, ^{4}J = 0.8 Hz, 3H), 2.22 (d, ^{4}J = 0.7 Hz, 3H), 1.14 (t, ^{3}J = 7.0 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 167.6, 162.6, 157.9, 157.0, 153.0, 145.2, 126.9, 122.2, 115.3, 112.4, 111.1, 44.6, 12.5, 12.2, 10.7, 7.8 ppm. HRMS calc. for $C_{20}H_{25}N_4O_3$ [M+H]$^+$: 369.1927, found 369.1929.

_N_-[4-(Diethylamino)phenyl]-3'-methyl-5-[2-(pyridin-2-yloxy)ethyl]-[3,5'-biisoxazole]-4'-carboxamide (SI74)



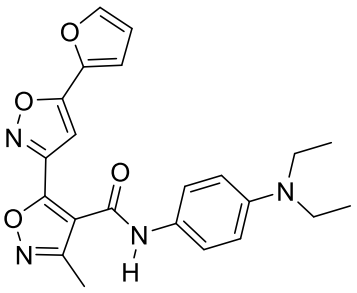
Synthesis according to the General procedure I. 3'-Methyl-5-[2-(pyridin-2-yloxy)ethyl]-[3,5'-biisoxazole]-4'-carboxylic acid hydrochloride (0.010 g, 0.0280 mmol), *N*,*N*-diethyl-*p*-phenylenediamine **17** (7.1 µL, 0.043 mmol, 1.5 equiv), HBTU (14 mg, 0.037 mmol, 1.3 equiv), DIPEA (0.010 mL, 0.057 mmol, 2.0 equiv), DMF (1 mL). Solvent for extraction: diethyl ether. Eluent for purification: *n*-heptane/EtOAc 4:1. Chromatography on silica gel gave compound **SI74** (8.3 mg, 0.0180 mmol, 63%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.59 (s, 1H), 8.15 (ddd, J = 5.1, 2.0, 0.8 Hz, 1H), 7.59 (ddd, J = 8.4, 7.1, 2.0 Hz, 1H), 7.53 (m$_c$, 1H), 6.90 (ddd, J = 7.1, 5.1, 1.0 Hz, 1H), 6.78–6.74 (m, 2H), 6.68 (m$_c$, 2H), 4.71 (t, ^{3}J = 6.2 Hz, 2H), 3.39 (t, ^{3}J = 6.2 Hz, 2H), 3.34 (q, ^{3}J = 7.0 Hz, 4H), 2.67 (s, 3H), 1.15 (t, ^{3}J = 7.0 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.4, 163.2, 162.9, 157.7, 155.7, 153.5, 146.8, 145.3, 138.9, 126.8, 122.3, 117.3, 114.6, 112.4, 111.2, 102.1, 62.0, 44.6, 27.0, 12.5, 12.4 ppm. HRMS calc. for $C_{25}H_{28}N_5O_4$ $[M+H]^+$: 462.2141, found 462.2140.

_N_-[4-(Diethylamino)phenyl]-5-ethyl-3'-methyl-[3,5'-biisoxazole]-4'-carboxamide (SI75)



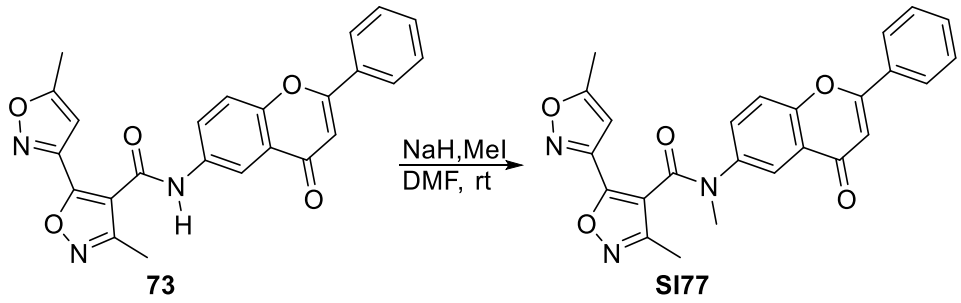
Synthesis according to the General procedure I. 5-Ethyl-3'-methyl-[3,5'-biisoxazole]-4'-carboxylic acid (5.0 mg, 0.023 mmol), *N*,*N*-diethyl-*p*-phenylenediamine **17** (5.6 µL, 0.034 mmol, 1.5 equiv), HBTU (11 mg, 0.029 mmol, 1.3 equiv), DIPEA (7.8 µL, 0.045 mmol, 2.0 equiv), DMF (0.5 mL). Solvent for extraction: diethyl ether. Eluent for purification: *n*-heptane/EtOAc 5:1. Chromatography on silica gel gave compound **SI75** (6.9 mg, 0.0187 mmol, 81%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.67 (s, 1H), 7.56 (m$_c$, 2H), 6.71 (m$_c$, 2H), 6.64 (s, 1H), 3.37 (q, ^{3}J = 7.0 Hz, 4H), 2.94 (qd, J = 7.6, 0.9 Hz, 2H), 1.43 (t, ^{3}J = 7.6 Hz, 3H), 2.70 (s, 3H), 1.18 (t, ^{3}J = 7.0 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 176.61, 163.19, 157.79, 155.92, 153.41, 145.30, 126.89, 122.30, 114.54, 112.41, 100.43, 44.59, 20.21, 12.53, 12.40, 11.55 ppm. HRMS calc. for $C_{20}H_{25}N_4O_3$ $[M+H]^+$: 369.1927, found 369.1928.

_N_-[4-(Diethylamino)phenyl]-5-(furan-2-yl)-3'-methyl-[3,5'-biisoxazole]-4'-carboxamide (SI76)



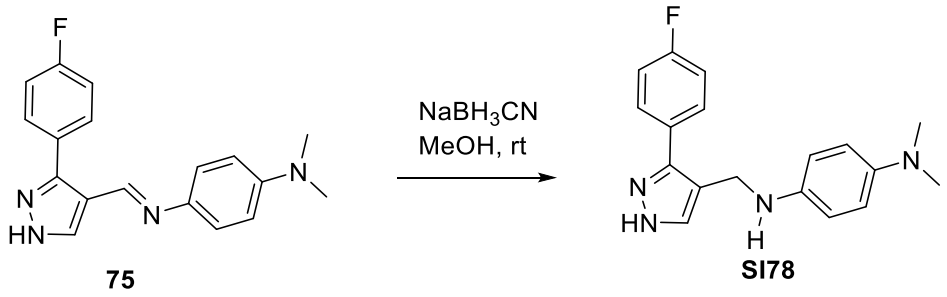
Synthesis according to the General procedure I. 5-(Furan-2-yl)-3'-methyl-[3,5'-biisoxazole]-4'-carboxylic acid (5.20 mg, 0.020 mmol), *N*,*N*-diethyl-*p*-phenylenediamine **17** (5.00 µL, 0.030 mmol, 1.5 equiv), HBTU (10.0 mg, 0.0260 mmol, 1.3 equiv), DIPEA (7.00 µL, 0.040 mmol, 2.0 equiv), DMF (0.5 mL). Solvent for extraction: diethyl ether. Eluent for purification: *n*-heptane/EtOAc 4:1. Chromatography on silica gel gave compound **SI76** (5.10 mg, 0.0125 mmol, 63%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.51 (s, 1H), 7.64 (dd, J = 1.8, 0.7 Hz, 1H), 7.55 (m$_c$, 2H), 7.07 (dd, J = 3.5 Hz, 0.8 Hz, 1H), 7.02 (s, 1H), 6.70 (m$_c$, 2H), 6.62 (dd, J = 3.5, 1.8 Hz, 1H), 3.35 (q, ^{3}J = 7.1 Hz, 4H), 2.69 (s, 3H), 1.16 (t, ^{3}J = 7.1 Hz, 6H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 163.3, 162.9, 157.6, 155.3, 153.7, 145.4, 141.8, 126.8, 122.3, 114.9, 112.4, 112.3, 112.3, 98.6, 44.6, 12.5, 12.4 ppm. HRMS calc. for $C_{25}H_{28}N_5O_4$ $[M+H]^+$: 407.1719, found 407.1718.

_N_,3',5-Trimethyl-_N_-(4-oxo-2-phenyl-4_H_-chromen-6-yl)-[3,5'-biisoxazole]-4'-carboxamide (SI77)



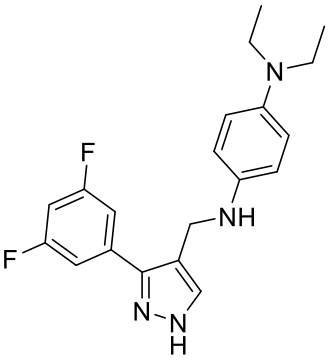
3',5-Dimethyl-*N*-(4-oxo-2-phenyl-4*H*-chromen-6-yl)-[3,5'-biisoxazole]-4'-carboxamide **73** (34.1 mg, 0.0798 mmol) was dissolved under argon in absolute DMF (1.5 mL). A 60% dispersion of sodium hydride in mineral oil (4.8 mg, 0.120 mmol, 1.5 equiv) was added and the reaction mixture was stirred for 1 h at room temperature. Iodomethane (9.90 µL, 0.160 mmol, 2 equiv) was added and the reaction mixture was stirred overnight at room temperature. The reaction mixture was diluted with ethyl acetate and washed three times with a mixture of water and brine (3:1). The solvent was removed with a rotary evaporator and the residue was subjected to automated preparative chromatography. The chromatography on silica gel was performed with an increasing gradient of ethyl acetate in *n*-hexane, starting with 0% of ethyl acetate gave compound **SI77** (20.8 mg, 0.0471 mmol, 59%) as fine white needles. M.p. 224.6–226.4 °C (decomp.). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.13–8.05 (m, 2H), 7.75–7.45 (m, 6H), 7.03 (s, 1H), 6.47 (bs, 1H), 3.43 (bs, 3H), 2.46 (s, 3H), 2.34 (s, 3H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 176.2, 171.9, 162.7, 160.6, 159.0, 156.0, 153.9, 151.0, 139.5, 132.5, 131.9, 130.9, 129.1, 126.4, 123.2, 121.6, 119.3, 114.9, 106.6, 100.6, 11.7, 9.9 ppm. HRMS calc. for $C_{25}H_{20}N_3O_5$ $[M+H]^+$: 442.1403, found 442.1405.

N^1-[[3-(4-Fluorophenyl)-1*H*-pyrazol-4-yl]methyl]-N^4,N^4-dimethylbenzene-1,4-diamine (SI78)



(*E*)-N^1-[[3-(4-Fluorophenyl)-1*H*-pyrazol-4-yl]methylene]-N^4,N^4-dimethylbenzene-1,4-diamine **75** (50.0 mg, 0.162 mmol) was dissolved in absolute methanol (0.50 mL). Sodium cyanoborohydride (10.2 mg, 0.162 mmol) was added, and the reaction mixture was stirred overnight at room temperature. A few drops of water were added and after 15 min the reaction mixture was diluted with ethyl acetate and washed three times with water. The solvent was removed with a rotary evaporator and the product mixture was purified by automated preparative chromatography. The chromatography on silica gel was performed with an increasing gradient of ethyl acetate in *n*-hexane, starting with 0% of ethyl acetate to give compound **SI78** (24.0 mg, 0.773 mmol, 48%) as a brownish oil. ^{1}H NMR (300 MHz, Acetone-d_6): δ 12.04 (bs, 1H), 7.87–7.79 (m, 2H), 7.71 (s, 1H), 7.22–7.11 (m, 2H), 6.73–6.64 (m$_c$, 4H), 4.41 (bs, 1H), 4.22 (s, 2H), 2.77 (s, 6H) ppm. ^{13}C NMR (75 MHz, Acetone-d_6): δ 163.1 (d, J = 244.7 Hz), 146.5 (br), 145.0, 142.2, 133.7 (br), 130.7 (br), 130.2 (d, J = 8.1 Hz), 117.1, 116.3, 116.1 (d, J = 21.5 Hz), 115.0, 42.3, 40.4 ppm. HRMS calc. for $C_{18}H_{20}FN_4$ $[M+H]^+$: 311.1672, found 311.1680.

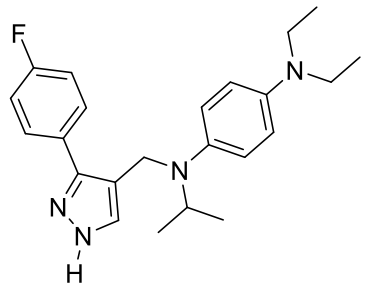
N^1-[(3-(3,5-Difluorophenyl)-1*H*-pyrazol-4-yl)methyl]-N^4,N^4-diethylbenzene-1,4-diamine (SI79)



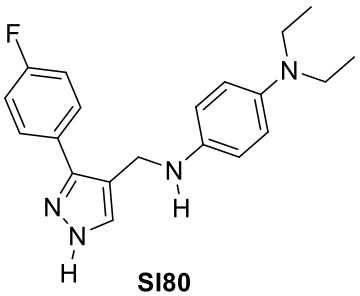
Synthesis according to the General procedure IX. Anhydrous sodium sulphate (215 mg, 1.51 mmol) was flame dried in an evacuated Schlenck flask. Absolute THF (2.5 mL), 3-(3,5-difluorophenyl)-1*H*-pyrazole-4-carbaldehyde (105 mg, 0.504 mmol), *N*,*N*-diethyl-*p*-phenylenediamine **17** (83.8 µL, 0.504 mmol) and acetic acid (28.9 µL, 0.504 mmol) were added. The reaction mixture was stirred at room temperature for 4 h and a 1.0 M solution of sodium cyanoborohydride in THF was added (2.02 mL, 2.02 mmol, 4 equiv). The reaction mixture was stirred at room temperature for 4 d and quenched with a saturated solution of sodium hydrogencarbonate in H_2O. After 20 min ethyl acetate and water were added, the phases were separated and the organic phase was washed twice with a mixture of water and brine (1:1). The solvent was removed with a rotary evaporator. The crude product was purified twice by automated preparative chromatography. The chromatographies on silica gel were performed with an increasing gradient of ethyl acetate in *n*-hexane, starting with 0% of ethyl acetate to yield compound **SI79** (83.5 mg, 0.234 mmol, 46%) as a brownish oil. ^{1}H NMR (300 MHz, acetone-d_6): δ 12.10 (bs, 1H), 7.80

(bs, 1H), 7.56–7.47 (m, 2H), 6.95 (tt, 1H, J = 2.4 Hz, J = 9.2 Hz), 6.70 (m_c, 4H), 4.26 (bs, 2H), 3.20 (q, 4H, ^3J = 7.0 Hz), 1.05 (t, 6H, ^3J = 7.0 Hz) ppm. ^{13}C NMR (75 MHz, acetone -d_6): δ 164.0 (dd, J = 13.4 Hz, J = 245.1 Hz), 146.7 (br), 142.0, 142.0, 142.0, 138.4, 132.8, 117.9, 117.7 (br), 115.4, 110.8 (m_c), 103.0 (t, J = 25.9 Hz), 46.3, 40.5, 13.0 ppm. HRMS calc. for $C_{20}H_{23}F_2N_4$ $[M+H]^+$: 357.1891, found 357.1891.

N^1,N^1-Diethyl-N^4-[(3-(4-fluorophenyl)-1*H*-pyrazol-4-yl)methyl]benzene-1,4-diamine (SI80) and N^1,N^1-diethyl-N^4-[(3-(4-fluorophenyl)-1*H*-pyrazol-4-yl)methyl]-N^4-isopropylbenzene-1,4-diamine (SI81)



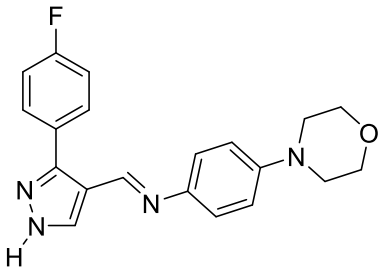
SI81



SI80

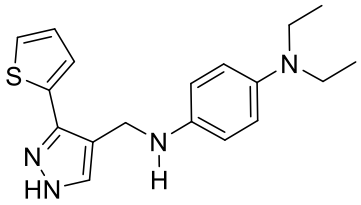
Synthesis according to the General procedure IX. Deviating from the General procedure IX, no sodium sulphate was used. Acetic acid (50.0 µL, 0.873 mmol), 3-(4-fluorophenyl)-1*H*-pyrazole-4-carbaldehyde (166 mg, 0.873 mmol), *N*,*N*-diethyl-*p*-phenylenediamine **17** (0.145 mL, 0.873 mmol), THF (4 mL), a 1.0 M solution of sodium cyanoborohydride in THF (4.37 mL, 4.37 mmol, 5 equiv, added 1 h later). Reaction time: 4 d; quenched with a saturated solution of $NaHCO_3$ in H_2O (5 mL) for 20 min. Solvents for extraction: ethyl acetate and a mixture of water and brine (3:1). Chromatography on silica gel gave compound **SI80** (84.7 mg, 0.250 mmol, 29%) as a slightly violet solid and compound **SI81** (70.8 mg, 0.209 mmol, 24%) as a violet oil. Compound **SI80**: ^{1}H NMR (300 MHz, acetone-d_6): δ 12.07 (bs, 1H), 7.8 4 (m_c, 2H), 7.72 (bs, 1H) , 7.18 (m_c, 2H), 6.68 (m_c, 4H), 4.38 (bs, 1H), 4.22 (s, 2H), 3.19 (q, 4H, ^3J = 7.0 Hz), 1.05 (t, 6H, ^3J = 7.0 Hz) ppm. ^{13}C NMR (75 MHz, Acetone-d_6): δ 163.2 (d, J = 244.7 Hz), 148.3, 142.3, 141.9, 130.2 (d, J = 8.0 Hz), 130.0, 128.2, 117.9, 117.1, 116.1 (d, J = 21.5 Hz), 115.2, 46.4, 40.5, 13.0 ppm. HRMS calc. for $C_{20}H_{24}FN_4$ $[M+H]^+$: 339.1985, found 339.1985. Compound **SI81**: ^{1}H NMR (300 MHz, Acetone-d_6): δ 11.90 (bs, 1H), 7.92 (m_c, 2H), 7.46 (s, 1H), 7.19 (m_c, 2H), 6.84, 6.61 (each m_c, each 2H), 4.23 (s, 2H), 3.68 (sep, 1H, J = 6.6 Hz), 3.25 (q, 4H, ^3J = 7.0 Hz), 1.10 (d, 6H, ^3J = 6.6 Hz), 1.07 (t, 6H, ^3J = 7.0 Hz) ppm. ^{13}C NMR (75 MHz, Acetone-d_6): δ 163.1 (d, J = 244.2 Hz), 144.0, 139.9, 134.0, 130.5 (d, J = 8.1 Hz), 130.4, 128.5, 123.5, 118.1, 115.8 (d, J = 21.4 Hz), 114.6, 52.2, 45.4, 44.0, 20.1, 13.0 ppm. HRMS calc. for $C_{23}H_{30}FN_4$ $[M+H]^+$: 381.2455, found 381.2457.

(*E*)-*N*-[[3-(4-Fluorophenyl)-1*H*-pyrazol-4-yl]methylene]-4-morpholinoaniline (SI82)



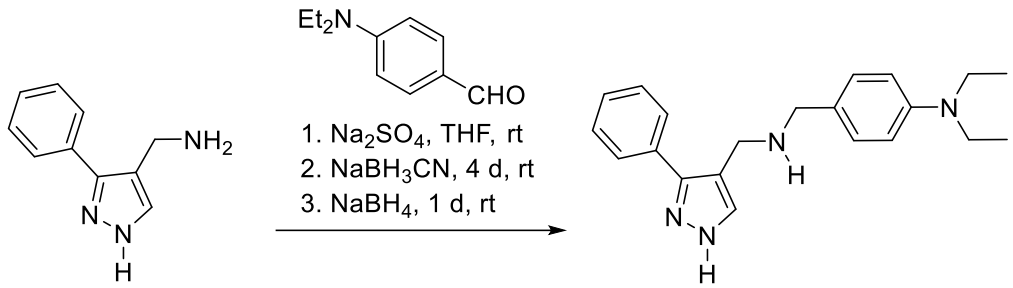
Synthesis according to the General procedure III. Deviating from the General procedure III, the reaction mixture was first stirred at room temperature overnight, then heated at 70 °C for 5 h and stirred at room temperature overnight. *p*-Toluenesulfonic acid and one additional equivalent of Na_2SO_4 were added, and the reaction mixture was heated at 90 °C for 4 h and at 70 °C overnight. 3-(4-Fluorophenyl)-1*H*-pyrazole-4-carboxaldehyde (95.1 mg, 0.500 mmol), 4-morpholinoaniline (89.1 mg, 0.500 mmol), Na_2SO_4 (142 mg + 71.0 mg, 1.00 mmol + 0.500 mmol), AcOH (5.7 µL, 0.10 mmol, 0.2 equiv), *p*-toluenesulfonic acid (9.5 mg, 0.050 mmol, 0.1 equiv), toluene (2 mL). Chromatography on silica gel gave compound **SI82** (62.0 mg, 0.177 mmol, 35%) as a brown solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.41 (s, 1H), 8.27 (s, 1H), 7.56 (m_c, 2H), 7.19–7.08 (m, 4H), 6.89 (m_c, 2H), 3.85 (m_c, 4H), 3.14 (m_c, 4H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.5 (d, J = 249.4 Hz), 150.5, 150.1, 144.2, 130.7 (d, J = 8.2 Hz), 122.0, 118.5, 118.2, 116.6, 116.4, 116.3 (d, J = 21.6 Hz), 67.1, 49.7 ppm. HRMS calc. for $C_{20}H_{20}FN_4O$ $[M+H]^+$: 351.1621, found 351.1622.

***N*^{1},*N*^{1}-Diethyl-*N*^{4}-[[3-(thiophen-2-yl)-1*H*-pyrazol-4-yl]methyl]benzene-1,4-diamine (SI83)**



Synthesis according to the General procedure IX. Deviating from the General procedure IX, the product was purified by two subsequent automated chromatography runs. Anhydrous sodium sulphate (120 mg), acetic acid (8.6 µL, 0.15 mmol, 0.5 equiv), 3-(thiophen-2-yl)-1*H*-pyrazole-4-carbaldehyde (53.7 mg, 0.301 mmol), *N*,*N*-diethyl-*p*-phenylenediamine **17** (50.1 µL, 0.301 mmol), THF (2 mL), a 1.0 M solution of sodium cyanoborohydride in THF (1.20 mL, 1.20 mmol, 4 equiv, added 1 h later). Reaction time: 2 d; quenched with a saturated solution of $NaHCO_3$ in H_2O (5 mL). Chromatography on silica gel gave compound **SI83** (41.9 mg, 0.128 mmol, 43%) as a greenish resin. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.73 (bs, 1H), 7.72, 7.44, 7.32, 7.08 (each br s, each 1H), 6.60 (m_c, 4H), 5.10 (t, 1H, ^3J = 5.3 Hz), 4.41 (d, 2H, ^3J = 5.1 Hz), 3.12 (q, 4H, ^3J = 7.0 Hz), 0.99 (t, 6H, ^3J = 7.0 Hz) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 143.4, 141.0, 139.9, 136.6, 129.5, 127.7, 124.5, 124.1, 116.5, 115.5, 113.7, 44.9, 30.6, 12.4 ppm. HRMS calc. for $C_{18}H_{23}N_4S$ $[M+H]^+$: 327.1643, found 327.1645.

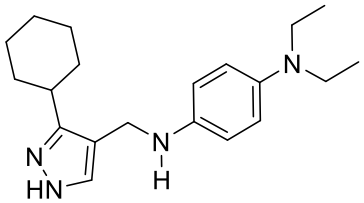
***N*,*N*-Diethyl-4-[[[(3-phenyl-1*H*-pyrazol-4-yl)methyl]amino]methyl]aniline (SI84)**



SI84

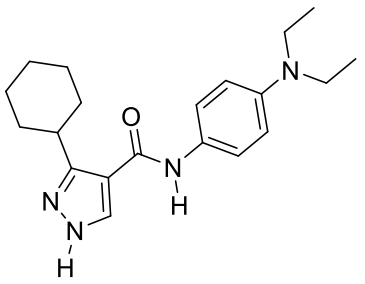
A mixture of 3-phenyl-1*H*-pyrazol-4-yl)methanamine (54.2 mg, 0.313 mmol), 4-(diethylamino)-benzaldehyde (77.6 mg, 0.438 mmol, 1.4 equiv) and sodium sulfate (133 mg, 0.939 mmol, 3 equiv) in anhydrous THF (3 mL) was stirred for 2 d at room temperature under argon. Sodium cyanoborohydride (49.2 mg, 0.783 mmol, 2.5 equiv) was added, and the reaction mixture was stirred for 3 d at room temperature. Sodium borohydride (11.8 mg, 0.313 mmol) was added, and the reaction mixture was stirred overnight at room temperature. The reaction mixture was diluted with ethyl acetate and washed three times with a mixture of water and brine (2:1). The solvent was removed with a rotary evaporator, and the crude product was purified by automated preparative chromatography. The chromatography on silica gel was performed with an increasing gradient of a mixture of ethyl acetate and 1% TEA in *n*-hexane, starting with 100% of *n*-hexane to give compound **SI84** (54.9 mg, 0.164 mmol, 52%) as white needles. M.p. 95.2–96.4 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.67 (bs, 1H), 7.78–7.66 (m, 2H), 7.62 (bs, 1H), 7.44–7.26 (m, 3H), 7.11 (m$_c$, 2H), 6.60 (m$_c$, 2H), 3.61 (s, 2H), 3.60 (s, 2H), 3.30 (q, 4H, ^{3}J = 7.0 Hz), 1.06 (t, 6H, ^{3}J = 7.0 Hz) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 146.3, 129.1, 128.3, 127.1, 127.0, 116.6, 111.5, 52.3, 43.6, 42.5, 12.4 ppm. HRMS calc. for $C_{21}H_{27}N_4$ $[M+H]^+$: 335.2236, found 335.2245.

***N*^{1}-[(3-Cyclohexyl-1*H*-pyrazol-4-yl)methyl]-*N*^{4},*N*^{4}-diethylbenzene-1,4-diamine (SI85)**



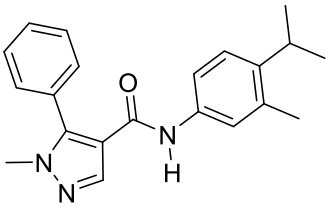
Synthesis according to the General procedure IX. Anhydrous sodium sulphate (120 mg), acetic acid (8.6 µL, 0.15 mmol, 0.5 equiv), 3-cyclohexyl-1*H*-pyrazole-4-carbaldehyde (53.8 mg, 0.302 mmol), *N*,*N*-diethyl-*p*-phenylenediamine **17** (50.2 µL, 0.302 mmol), THF (3 mL), a 1.0 M solution of sodium cyanoborohydride in THF (1.21 mL, 1.21 mmol, 4 equiv, added 1 h later). Reaction time: 2 d; quenched with a saturated solution of $NaHCO_3$ in H_2O (5 mL). Chromatography on silica gel gave compound **SI85** (31.6 mg, 0.0872 mmol, 29%) as a brown resin. ^{1}H NMR (300 MHz, Acetone-d_6): δ 11.44 (bs, 1H), 7.43 (s, 1H), 6.72–6.10 (m, 4H), 4.08 (s, 1H), 3.17 (q, 4H, ^{3}J = 7.0 Hz), 2.80 (tt, 1H, J = 3.5 Hz, J = 11.9 Hz), 1.93–1.17 (m, 10H), 1.03 (t, 6H, ^{3}J = 7.0 Hz) ppm. ^{13}C NMR (75 MHz, Acetone-d_6): δ 142.8, 141.61, 135.2, 118.3, 115.8, 115.0, 46.5, 39.8, 36.3, 33.6, 27.4, 26.9, 13.0 ppm. HRMS calc. for $C_{20}H_{31}N_4$ $[M+H]^+$: 327.2549, found 327.2549.

3-Cyclohexyl-*N*-[4-(diethylamino)phenyl]-1*H*-pyrazole-4-carboxamide (SI86)



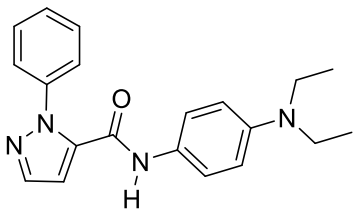
Synthesis according to the General procedure I. 3-Cyclohexyl-1*H*-pyrazole-4-carboxylic acid (0.100 g, 0.515 mmol), *N*,*N*-diethyl-*p*-phenylenediamine **17** (85.6 μL, 0.515 mmol), HBTU (254 mg, 0.670 mmol, 1.3 equiv), DIPEA (0.179 mL, 1.03 mmol, 2 equiv), DMF (3 mL). Solvent for extraction: ethyl acetate and a mixture of water and brine (1:1). Chromatography on silica gel gave compound **SI86** (102 mg, 0.300 mmol, 58%) as a white solid. M.p. 153.9–155.4 °C. ^{1}H NMR (300 MHz, Acetone-d_6): δ 12.03 (bs, 1H), 8.74 (s, 1H), 8.02 (s, 1H), 7.52 (m$_c$, 2H), 6.68 (m$_c$, 2H), 3.54 (tt, 1H, J = 3.4 Hz, J = 12.0 Hz), 3.35 (q, 4H, ^{3}J = 7.0 Hz), 2.03–1.94 (m, 2H), 1.86–1.20 (m, 8H), 1.12 (t, 6H, ^{3}J = 7.0 Hz) ppm. ^{13}C NMR (75 MHz, Acetone-d_6): δ 162.5, 154.0 (br), 145.4, 136.6 (br), 129.6, 122.6, 114.4, 113.2, 45.1, 36.0, 32.9, 27.4, 26.9, 12.9 ppm. HRMS calc. for $C_{20}H_{29}N_4O$ $[M+H]^+$: 341.2341, found 341.2347.

***N*-(4-Isopropyl-3-methylphenyl)-1-methyl-5-phenyl-1*H*-pyrazole-4-carboxamide (SI87)**



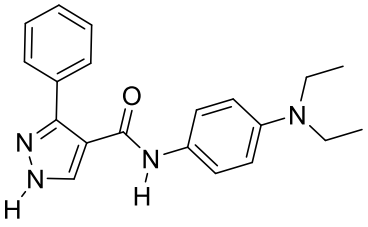
Synthesis according to the General procedure I. 1-Methyl-5-phenyl-1*H*-pyrazole-4-carboxylic acid **46e** (38.4 mg, 0.190 mmol), *N*-ethyl-*N*-isopropylphenylenediamine hydrochloride (35.3 mg, 0.190 mmol), HBTU (93.7 mg, 0.247 mmol, 1.3 equiv), DIPEA (99.3 μL, 0.570 mmol, 2 equiv), DMF (1 mL). Solvent for extraction: diethyl ether. Chromatography on silica gel gave compound **SI87** (40.8 mg, 0.122 mmol, 64%) as a white solid. M.p. 153.0–154.3 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.55 (s, 1H), 8.12 (s, 1H), 7.53–7.42 (m, 5H), 7.40–7.32 (m, 2H), 7.11 (d, 1H, ^{3}J = 8.3 Hz), 3.68 (s, 3H), 3.02 (sep, 1H, ^{3}J = 6.8 Hz), 2.23 (s, 3H), 1.13 (d, 6H, ^{3}J = 6.8 Hz) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.0, 144.4, 141.7, 138.5, 137.0, 135.0, 130.5, 129.6, 129.3, 128.6, 125.0, 121.9, 118.3, 116.6, 37.6, 28.7, 23.6, 19.5 ppm. HRMS calc. for $C_{21}H_{24}N_3O$ $[M+H]^+$: 334.1919, found 334.1919.

***N*-[4-(Diethylamino)phenyl]-1-phenyl-1*H*-pyrazole-5-carboxamide (SI88)**



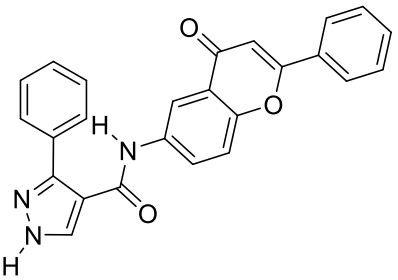
Synthesis according to the General procedure I. 1-Phenyl-1*H*-pyrazole-5-carboxylic acid (51.2 mg, 0.272 mmol), *N*,*N*-diethyl-*p*-phenylenediamine **17** (45.2 μL, 0.272 mmol), HBTU (134 mg, 0.354 mmol, 1.3 equiv), DIPEA (94.4 μL, 0.544 mmol, 2 equiv), DMF (2 mL). Solvent for extraction: diethyl ether. Recrystallization (MeOH/H_2O 10+1) without chromatography on silica gel gave compound **SI88** (63.0 mg, 0.188 mmol, 69%) as yellow needles. M.p. 129.3–130.7 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.21 (s, 1H), 7.77 (d, 1H, ^{3}J = 1.9 Hz), 7.50–7.35 (m, 7H), 6.97 (d, 1H, ^{3}J = 1.9 Hz), 6.62 (m$_c$, 2H), 3.29 (q, 4H, ^{3}J = 7.0 Hz), 1.06 (t, 6H, ^{3}J = 7.0 Hz) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 157.3, 144.5, 140.0, 139.4, 137.6, 128.7, 127.5, 126.9, 124.1, 121.8, 111.7, 109.0, 43.7, 12.3 ppm. HRMS calc. for $C_{20}H_{23}N_4O$ $[M+H]^+$: 335.1872, found 335.1875.

N-[4-(Diethylamino)phenyl]-3-phenyl-1*H*-pyrazole-4-carboxamide (SI89)



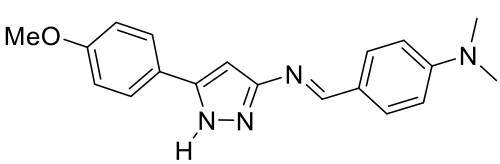
Synthesis according to the General procedure I. Deviating from the General procedure I, the reaction was performed under a microwave heating (70 °C, 60 min). 3-Phenyl-1*H*-pyrazole-4-carboxylic acid (188 mg, 1.00 mmol), *N*,*N*-diethyl-*p*-phenylenediamine hydrochloride **50** (236 mg, 1.18 mmol, 1.2 equiv), HBTU (493 mg, 1.30 mmol, 1.3 equiv), DIPEA (0.871 mL, 5.00 mmol, 5 equiv), DMF (4 mL). Solvent for extraction: ethyl acetate. Automated chromatography on silica gel gave compound **SI89** (83.0 mg, 0.248 mmol, 25%) as an amorphous white solid. ^{1}H NMR (300 MHz, Acetone-d_6): δ 12.44 (bs, 1H), 8.66 (bs, 1H), 8.13 (bs, 1H), 7.89–7.82 (m, 2H), 7.50–7.33 (m, 5H), 6.66 (m$_c$, 2H), 3.35 (q, 4H, ^{3}J = 7.0 Hz), 1.12 (t, 3H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 162.1, 145.5, 129.6, 129.6, 129.4, 129.1, 129.0, 128.8, 128.6, 122.4, 117.0, 113.1, 45.1, 12.9 ppm. ^{1}H NMR (300 MHz, DMSO-d_6): δ 13.27 (bs, 1H), 9.58 (s, 1H), 8.15 (bs, 1H), 7.77–7.71 (m, 2H), 7.45–7.32 (m, 5H), 6.61 (m$_c$, 2H), 3.29 (q, 4H, ^{3}J = 7.0 Hz), 1.06 (t, 3H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.3, 144.0, 128.2, 128.0, 127.9, 121.8, 115.2, 111.9, 43.7, 12.3 ppm. HRMS calc. for $C_{20}H_{23}N_4O$ $[M+H]^+$: 335.1872, found 335.1882.

N-(4-Oxo-2-phenyl-4*H*-chromen-6-yl)-3-phenyl-1*H*-pyrazole-4-carboxamide (SI90)



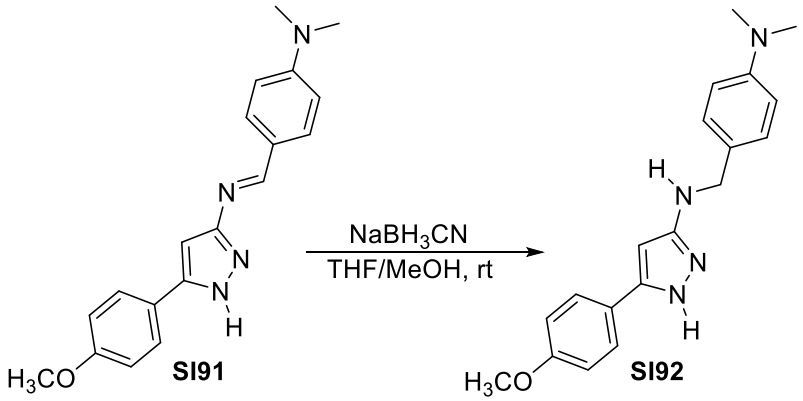
Synthesis according to the General procedure I. Deviating from the General procedure I, the reaction time was 7 d. 3-Phenyl-1*H*-pyrazole-4-carboxylic acid (99.5 mg, 0.529 mmol), 6-aminoflavone (126 mg, 0.529 mmol), HBTU (261 mg, 0.688 mmol, 1.3 equiv), DIPEA (0.184 mL, 1.06 mmol, 2 equiv), DMF (3 mL). Solvent for extraction: ethyl acetate and brine. Chromatography on silica gel gave compound **SI90** (41.0 mg, 0.101 mmol, 19%) as a yellow solid. M.p. 272.4–276.2 °C (decomp.). ^{1}H NMR (300 MHz, DMSO-d_6): δ 13.65–13.10 (bd, 1H), 10.25 (s, 1H), 8.45 (d, 1H, ^{4}J = 2.6 Hz), 8.42–8.20 (bs, 1H), 8.15–8.03 (m, 3H), 7.82–7.72 (m, 3H), 7.65–7.54 (m, 3H), 7.50–7.34 (bm, 3H), 7.01 (s, 1H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 176.9, 162.3, 162.1 (b), 151.6, 136.8, 136.7, 131.7, 131.2, 129.1, 128.4, 128.0, 126.3, 126.2, 123.4, 118.8, 114.3 (b), 113.9, 106.4, 10.2 ppm. HRMS calc. for $C_{25}H_{18}N_3O_3$ $[M+H]^+$: 408.1348, found 408.1349.

(*E*)-*N*-[4-(Dimethylamino)benzylidene]-5-(4-methoxyphenyl)-1*H*-pyrazol-3-amine (SI91)



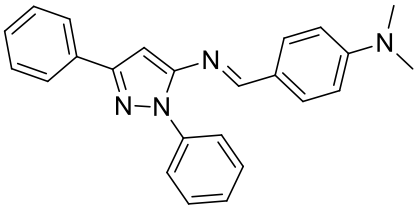
Synthesis according to the General procedure III. 4-(Dimethylamino)benzaldehyde (74.6 mg, 0.500 mmol), 3-amino-5-(4-methoxyphenyl)pyrazole (94.6 mg, 0.500 mmol), Na_2SO_4 (142 mg, 1.00 mmol), AcOH (5.7 µL, 0.10 mmol, 0.2 equiv), toluene (2 mL). Chromatography on silica gel gave compound **SI91** (101 mg, 0.315 mmol, 63%) as a yellow solid. M.p. 163.7–164.8 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.82 (bs, 1H), 8.69 (bs, 1H), 7.80–7.65 (m, 4H), 7.00 (bs, 2H), 6.79 (m$_c$, 2H), 6.64 (s, 1H), 3.79 (s, 3H), 3.01 (s, 6H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 160.2, 159.1, 152.4, 150.2, 142.7, 123.8, 122.1, 130.0, 126.2, 111.0, 114.2, 111.5, 55.1, 39.6 ppm. HRMS calc. for $C_{19}H_{21}N_4O$ [M+H]$^+$: 321.1715, found 321.1717.

***N*-[4-(Dimethylamino)benzyl]-5-(4-methoxyphenyl)-1*H*-pyrazol-3-amine (SI92)**



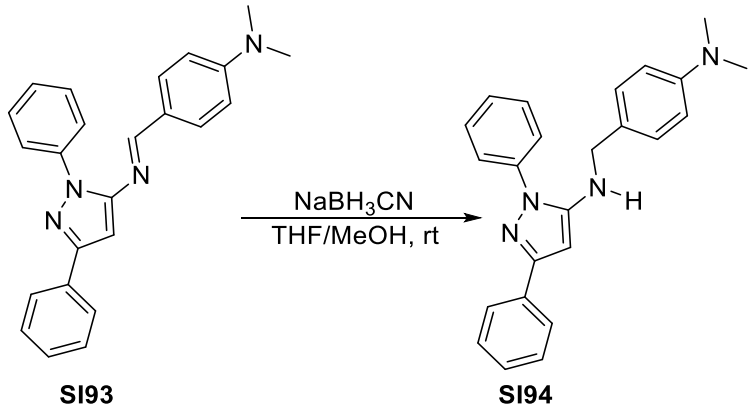
(*E*)-*N*-[4-(Dimethylamino)benzylidene]-5-(4-methoxyphenyl)-1*H*-pyrazol-3-amine **SI91** (49.3 mg, 154 mmol) was dissolved under argon in a mixture of THF (1.3 mL) and MeOH (0.80 mL). Sodium cyanoborohydride (23.3 mg, 0.615 mmol, 4 equiv) was added, and the reaction mixture was stirred for 5 d at room temperature. A saturated solution of sodium hydrogen carbonate in H_2O (5mL) was added and 20 min later EtOAc and water. The phases were separated and the organic phase was washed twice with water. The solvent was removed with a rotary evaporator and the residue was subjected to automated preparative chromatography. The chromatography on silica gel was performed with an increasing gradient of ethyl acetate in *n*-hexane, starting with 0% of ethyl acetate gave compound **SI92** (39.6 mg, 0.123 mmol, 80%) as a beige solid. M.p. 154.4–158.3 °C. ^{1}H NMR (300 MHz, Acetone-d_6): δ 10.95 (bs, 1H), 7.62 (m$_c$, 2H), 7.25 (m$_c$, 2H), 6.94 (m$_c$, 2H), 6.70 (m$_c$, 2H), 5.83 (s, 1H), 4.79 (bs, 1H), 4.23 (s, 2H), 3.81 (s, 3H), 2.89 (s, 6H) ppm. ^{13}C NMR (75 MHz, Acetone-d_6): δ 160.2, 156.9 (br), 150.9, 146.2 (br), 129.7, 129.4, 127.1, 125.7, 87.3, 114.9, 113.4, 55.6, 49.2, 40.8 ppm. HRMS calc. for $C_{19}H_{23}N_4O$ [M+H]$^+$: 323.1872, found 323.1873.

(*E*)-*N*-[4-(Dimethylamino)benzylidene]-1,3-diphenyl-1*H*-pyrazol-5-amine (SI93)



Synthesis according to the General procedure III. Deviating from the General procedure III, the reaction mixture was first heated at 70 °C for 3 h. Then *p*-toluenesulfonic acid was added and the reaction mixture was heated at 70 °C for 2 h. 4-(Dimethylamino)benzaldehyde (74.6 mg, 0.500 mmol), 5-amino-1,3-diphenyl-1*H*-pyrazole (118 mg, 1.00 mmol), Na_2SO_4 (142 mg, 1.00 mmol), AcOH (5.7 µL, 0.10 mmol, 0.2 equiv), *p*-toluenesulfonic acid (9.5 mg, 0.050 mmol, 0.1 equiv), toluene (2 mL). Recrystallization (toluene/hexane 1+1) after chromatography on silica gel gave compound **SI93** (107 mg, 0.292 mmol, 58%) as yellow needles. M.p. 170.1–171.6 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.76 (s, 1H), 7.94–7.84 (m, 4H), 7.74 (m_c, 2H), 7.57–7.32 (m, 2H), 7.00 (s, 1H), 6.82 (m_c, 2H), 3.03 (s, 6H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.6, 152.9, 152.3, 150.2, 139.4, 133.1, 130.7, 128.6, 128.6, 127.9, 126.3, 125.1, 123.4, 122.9, 111.5, 90.6, 39.6 ppm. HRMS calc. for $C_{24}H_{23}N_4$ $[M+H]^+$: 367.1923, found 367.1922.

***N*-[4-(Dimethylamino)benzyl]-1,3-diphenyl-1*H*-pyrazol-5-amine (SI94)**

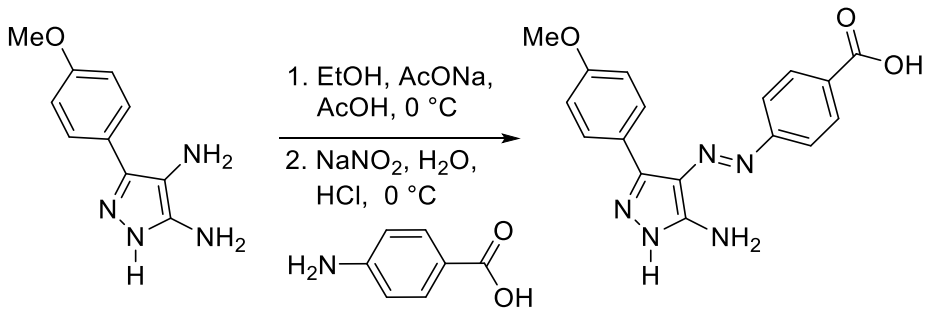


SI93 **SI94**

(*E*)-*N*-[4-(Dimethylamino)benzylidene]-1,3-diphenyl-1*H*-pyrazol-5-amine **SI93** (62.5 mg, 171 mmol) was dissolved under argon in a mixture of THF (1.3 mL) and MeOH (0.80 mL). Sodium cyanoborohydride (25.8 mg, 0.682 mmol, 4 equiv) was added, and the reaction mixture was stirred for 5 d at room temperature. A saturated solution of sodium hydrogen carbonate in H_2O (5mL) was added and 20 min later EtOAc and water. The phases were separated and the organic phase was washed twice with water. The solvent was removed with a rotary evaporator and the residue was subjected to automated preparative chromatography. The chromatography on silica gel with an increasing gradient of ethyl acetate in *n*-hexane, starting with 0% of ethyl acetate, gave compound **SI94** (62.1 mg, 0.169 mmol, 99%) as a beige solid. M.p. 127.3–129.4 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.75–7.70 (m, 2H), 7.66–7.61 (m, 2H), 7.55–7.47 (m, 2H), 7.39–7.31 (m, 3H), 7.30–7.20 (m, 3H), 6.70–6.64 (m, 2H), 5.97 (t, 1H, J = 5.8 Hz), 5.95 (s, 1H), 4.14 (d, 2H, J = 5.8 Hz), 2.83 (s, 6H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 150.0, 149.6, 149.5, 139.2, 133.5, 129.2, 128.4, 128.3,

127.5, 126.9, 126.5, 125.0, 123.3, 112.3, 85.6, 48.2, 40.2 ppm. HRMS calc. for $C_{24}H_{25}N_4$ $[M+H]^+$: 369.2079, found 369.2076.

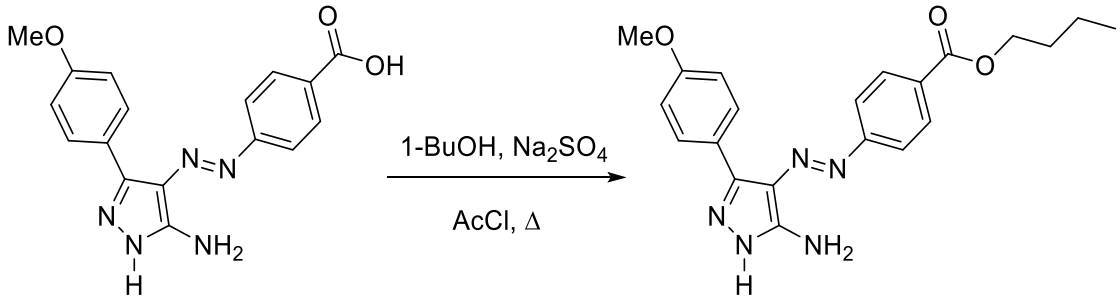
(*E*)-4-[[5-Amino-3-(4-methoxyphenyl)-1*H*-pyrazol-4-yl]diazenyl]benzoic acid (SI95)



SI95

3-(4-Methoxyphenyl)-1*H*-pyrazol-5-amine (189 mg, 1.00 mmol) was dissolved in ethanol (12.5 mL). To this solution, sodium acetate (246 mg, 3.00 mmol, 3 equiv) and acetic acid (0.172 mL, 3.00 mmol, 3 equiv) were added, and the solution was cooled to 0 °C in an ice bath. Further, a solution of sodium nitrite (79.4 mg, 1.15 mmol) in water (1.5 mL) was prepared and cooled to 0 °C. 4-Aminobenzoic acid (158 mg, 1.15 mmol) was dissolved in an equimixture of conc. hydrochloric acid and water (3.0 mL) and cooled to 0 °C in an ice bath. To this white slurry, the sodium nitrite solution was added slowly at 0 °C during a period of 20 min via a syringe. This mixture was added during a period of 30 min to the 3-(4-methoxyphenyl)-1*H*-pyrazol-5-amine solution via a syringe. Simultaneously three portions of sodium acetate (246 mg, 246 mg and 492 mg) were added to the reaction mixture after 10 min, 20 min and 30 min, respectively. The reaction mixture was stirred for 70 min. Ethyl acetate was added, and the organic phase was washed once with water and extracted twice with a 0.5 M solution of sodium hydroxide in water. The aqueous phase was neutralized with 1 M hydrochloric acid and the resulting suspension was filtered. The crude solid material was dried *in vacuo* and purified by automated preparative chromatography. The chromatography on silica gel was performed with an increasing gradient of methanol in ethyl acetate, starting with 0% of methanol, increasing to 10% methanol and long isocratic continuation with 10% methanol to give compound **SI95** (131 mg, 0.388 mmol, 39%) as an orange resin. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.53 (bs, 2H), 8.09–8.00 (m, 4H), 7.78 (m_c, 2H), 7.20 (bs, 2H), 7.06 (m_c, 2H), 3.82 (s, 3H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 167.2, 159.4, 155.9, 130.4, 129.9, 128.7, 124.0, 122.9, 120.6, 113.9, 55.1 ppm. HRMS calc. for $C_{17}H_{16}N_5O_3$ $[M+H]^+$: 338.1253, found 338.1252.

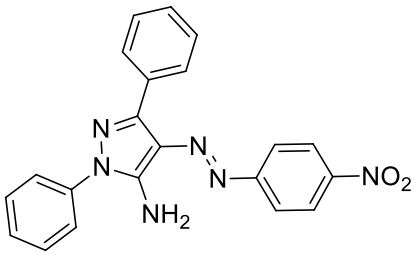
(*E*)-Butyl 4-[[5-amino-3-(4-methoxyphenyl)-1*H*-pyrazol-4-yl]diazenyl]benzoate (SI96)



SI95 **SI96**

(*E*)-4-[[5-Amino-3-(4-methoxyphenyl)-1*H*-pyrazol-4-yl]diazenyl)]benzoic acid **SI95** (40.0 mg, 0.119 mmol) was dissolved in 1-butanol (2 mL). Anhydrous sodium sulfate (400 mg) and acetyl chloride (27.7 μL, 0.390 mmol) were added, and the reaction mixture was refluxed for 7 h. Water and ethyl acetate were added and the phases were separated. The organic phase was washed three times with a 5% solution of sodium hydrogen carbonate in water and three times with water until the water remained neutral. The solvent was removed with a rotary evaporator, and the crude product was purified by automated chromatography on silica gel, using a gradient of increasing ethyl acetate starting with 100% *n*-hexane to give compound **SI96** (13.7 mg, 0.0348 mmol, 29%) as an orange resin. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.11 (bs, 1H), 8.10–8.01 (m, 4H), 7.81 (m$_c$, 2H), 7.43 (bs, 2H), 7.06 (m$_c$, 2H), 4.29 (t, 2H, ^{3}J = 6.5 Hz), 3.82 (s, 3H), 1.77–1.66 (m, 2H), 1.51–1.38 (m, 2H), 0.95 (t, 3H, ^{3}J = 7.4 Hz) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 165.4, 159.5, 156.3, 132.7, 131.2, 130.2, 129.0, 128.7, 128.2, 120.8, 113.9, 64.3, 55.1, 30.2, 18.7, 13.5 ppm. HRMS calc. for $C_{21}H_{24}N_5O_3$ $[M+H]^+$: 394.1879, found 394.1882.

(*E*)-4-[(4-Nitrophenyl)diazenyl]-1,3-diphenyl-1*H*-pyrazol-5-amine (SI97)

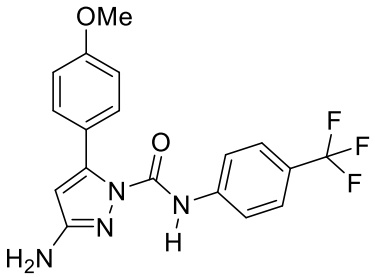


5-Amino-1,3-diphenyl-1*H*-pyrazole (0.100 g, 0.425 mmol) was dissolved in ethanol (3 mL). To this solution, sodium acetate (105 mg, 1.28 mmol, 3 equiv) and acetic acid (72.9 μL, 1.28 mmol, 3 equiv) were added, and the resulting solution was cooled to 0 °C in an ice bath. A solution of sodium nitrite (29.3 mg, 0.425 mmol) in water (0.5 mL) was prepared and cooled to 0 °C. *p*-Nitroaniline (58.7 mg, 0.425 mmol) was dissolved in an equimixture of concentrated hydrochloric acid and water (1 mL) and cooled to 0 °C in an ice bath. To this solution, the sodium nitrite solution was added slowly during a period of 30 min. After stirring the reaction mixture for 10 min, it was added during a period of 15 min to the 5-amino-1,3-diphenyl-1*H*-pyrazole solution in ethanol. Simultaneously, sodium acetate (800 mg) was added to the reaction mixture in small portions. The reaction mixture was stirred for 2 h. Ethyl acetate was added, and the organic phase was washed three times with water. The organic solvents were removed with a rotary evaporator, and the crude product was purified by column chromatography on silica gel (toluene/ethyl acetate 4:1). The product was recrystallized from a mixture of 2-propanol (12 mL) and ethyl acetate (2 mL) to yield compound **SI97** (108 mg, 0.281 mmol, 66%) as orange crystals. M.p. 209.7–211.1

°C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.34 (m, 2H), 8.18–8.13 (m, 2H), 8.08 (s, 2H), 7.96 (m, 2H), 7.72–7.42 (m, 8H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 157.2, 148.8, 145.8, 139.8, 137.2, 131.5, 129.6, 128.9, 128.5, 128.1, 127.9, 125.0, 124.1, 123.4, 121.5 ppm. HRMS calc. for $C_{21}H_{17}N_6O_2$ $[M+H]^+$: 385.1413, found 385.1412.

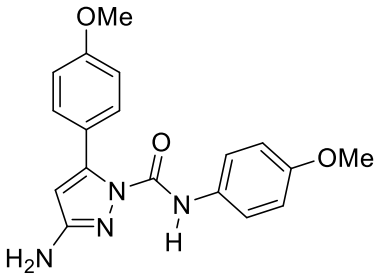
1-[5-(4-Methoxyphenyl)-1*H*-pyrazol-3-yl]-3-[4-(trifluoromethyl)phenyl]urea (SI98)

Synthesis according to the General procedure IV. Deviating from the General procedure IV, anhydrous tetrahydrofuran was used as a solvent. 3-Amino-5-(4-methoxyphenyl)pyrazole (94.6 mg, 0.500 mmol), 4-(trifluoromethyl)phenyl isocyanate (71.4 μL, 0.500 mmol), THF (1.5 mL). Automated chromatography on silica gel gave compound **SI98** (149 mg, 0.396 mmol, 79%) as fine white needles. M.p. 213.6–214.8 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.35 (s, 1H), 7.76–7.68 (m, 4H), 7.65–7.59 (m, 2H), 6.94 (m_c, 2H), 5.71 (s, 1H), 5.50 (s, 2H), 3.84 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.8, 153.3, 150.7, 150.4, 140.3, 127.8, 126.6 (q, J = 3.8 Hz), 124.9, 124.3 (q, J = 271.6 Hz), 119.6, 114.3, 87.0, 55.6 ppm. HRMS calc. for $C_{18}H_{16}F_3N_4O_2$ $[M+H]^+$: 377.1225, found 377.1220.

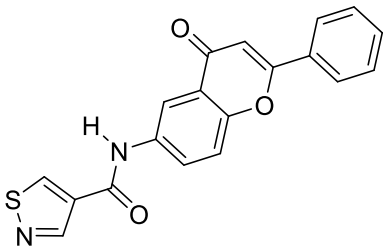


3-Amino-*N*,5-bis(4-methoxyphenyl)-1*H*-pyrazole-1-carboxamide (SI99)

Synthesis according to the General procedure IV. Deviating from the General procedure IV, anhydrous tetrahydrofuran was used as a solvent. 3-Amino-5-(4-methoxyphenyl)pyrazole (94.6 mg, 0.500 mmol), 4-methoxyphenyl isocyanate (64.4 μL, 0.500 mmol), THF (2 mL). Automated chromatography on silica gel gave compound **SI99** (145 mg, 0.428 mmol, 86%) as a white solid. M.p. 216.5–218.3 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.79 (s, 1H), 7.86 (m_c, 2H), 7.59 (m_c, 2H), 6.99 (m_c, 2H), 6.95 (m_c, 2H), 6.54 (s, 2H), 5.76 (s, 1H), 3.80 (s, 3H), 3.75 (s, 3H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 159.7, 155.9, 151.5, 151.4, 150.6, 130.2, 127.4, 124.9, 122.7, 113.8, 84.6 , 55.2, 55.1 ppm. HRMS calc. for $C_{18}H_{19}N_4O_3$ $[M+H]^+$: 339.1457, found 339.1459.

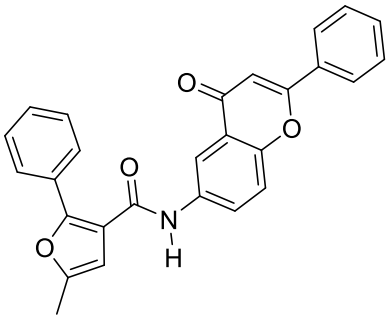


_N_-(4-Oxo-2-phenyl-4_H_-chromen-6-yl)isothiazole-4-carboxamide (SI100)



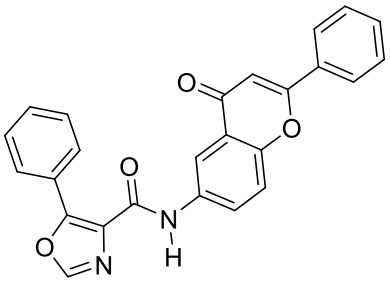
Synthesis according to the General procedure I. Isothiazole-4-carboxylic acid **46s** (32.3 mg, 0.250 mmol), 6-aminoflavone **5g** (59.3 mg, 0.250 mmol), HBTU (123 mg, 0.325 mmol, 1.3 equiv), DIPEA (87.1 μL, 0.500 mmol, 2 equiv), DMF (1.5 mL). Solvent for extraction: ethyl acetate and water containing 50% brine. Chromatography on silica gel gave compound **SI100** (33.4 mg, 0.0959 mmol, 38%) as a yellow solid. M.p. 283.6–288.5 °C (decomp.). ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.72 (s, 1H), 9.30 (d, 1H, ^{4}J = 2.0 Hz), 8.67 (d, 1H, ^{4}J = 2.7 Hz), 8.56 (d, 1H), 8.24 (dd, 1H, ^{3}J = 9.1 Hz), 8.15–8.08 (m, 2H), 7.81 (d, 1H), 7.66–7.56 (m, 3H), 7.03 (s, 1H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 176.9, 162.3, 159.3, 155.1, 152.0, 150.3, 136.0, 131.7, 131.2, 129.1, 127.1, 126.3, 125.9, 123.4, 118.8, 114.9, 106.5 ppm. HRMS calc. for $C_{19}H_{13}N_2O_3S$ $[M+H]^+$: 349.0647, found 349.0649.

5-Methyl-_N_-(4-oxo-2-phenyl-4_H_-chromen-6-yl)-2-phenylfuran-3-carboxamide (SI101)



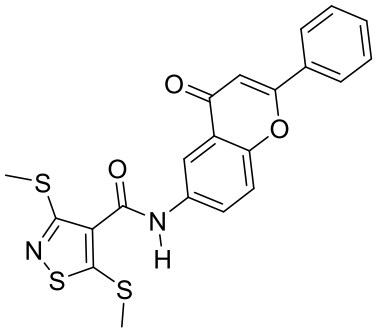
Synthesis according to the General procedure I. Deviating from the General procedure I, the reaction time was 3 d. 5-Methyl-2-phenylfuran-3-carboxylic acid (31.9 mg, 0.158 mmol), 6-aminoflavone **5g** (37.4 mg, 0.158 mmol), HBTU (77.9 mg, 0.205 mmol, 1.3 equiv), DIPEA (55.0 μL, 0.316 mmol, 2 equiv), DMF (1 mL). Solvent for extraction: ethyl acetate and a mixture of water and brine (2:1). Chromatography on silica gel gave compound **SI101** (27.1 mg, 0.0643 mmol, 41%) as a slightly yellow solid. M.p. 217.3–219.7 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.37 (s, 1H), 8.49 (d, 1H, ^{4}J = 2.7 Hz), 8.14–8.07 (m, 3H), 7.87–7.82 (m, 2H), 7.79 (d, 1H, ^{3}J = 9.1 Hz), 7.66–7.55, 7.48–7.32 (each m, each 3H), 7.02 (s, 1H), 6.70 (q≈d, 1H, ^{4}J = 1.1 Hz), 2.40 (d, 3H, ^{4}J = 1.0 Hz) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 176.9, 162.4, 162.3, 151.8, 151.5, 150.9, 136.5, 131.7, 131.1, 129.7, 129.1, 128.3, 126.5, 126.5, 126.3, 123.4, 118.9, 118.5, 114.3, 108.2, 106.5, 13.1 ppm. HRMS calc. for $C_{27}H_{20}NO_4$ $[M+H]^+$: 422.1392, found 422.1392.

_N_-(4-Oxo-2-phenyl-4_H_-chromen-6-yl)-5-phenyloxazole-4-carboxamide (SI102)



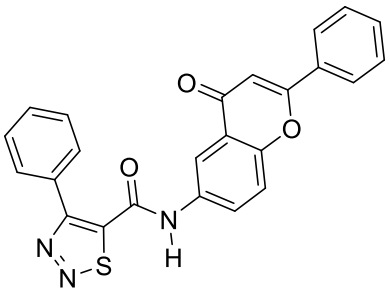
Synthesis according to the General procedure I. 5-Phenyloxazole-4-carboxylic acid **46a** (44.7 mg, 0.236 mmol), 6-aminoflavone **5g** (56.1 mg, 0.236 mmol), HBTU (116 mg, 0.307 mmol, 1.3 equiv), DIPEA (82.2 μL, 0.472 mmol, 2 equiv), DMF (2 mL). Solvent for extraction: ethyl acetate and a mixture of water and brine (2:1). Chromatography on silica gel gave compound **SI102** (28.9 mg, 0.0708 mmol, 30%) as a yellow solid. M.p. 227.3–228.8 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.61 (s, 1H), 8.72 (s, 1H), 8.69 (d, 1H, ^{4}J = 2.6 Hz), 8.23–8.17 (m, 3H), 8.14–8.07 (m, 2H), 7.80 (d, 1H, ^{3}J = 9.1 Hz), 7.65–7.48 (m, 6H), 7.04 (s, 1H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 176.9, 162.3, 159.7, 152.2, 152.0, 150.3, 135.9, 131.7, 131.1, 130.1, 129.1, 128.7, 128.5, 127.9, 127.2, 126.7, 126.3, 123.4, 118.8, 114.9, 106.5 ppm. HRMS calc. for $C_{25}H_{17}N_2O_4$ $[M+H]^+$: 409.1188, found 409.1187.

3,5-Bis(methylthio)-_N_-(4-oxo-2-phenyl-4_H_-chromen-6-yl)isothiazole-4-carboxamide (SI103)



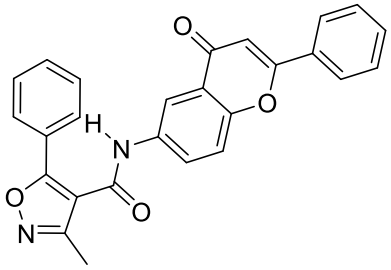
Synthesis according to the General procedure I. Deviating from the General procedure I, the reaction time was 3 d at room temperature. 3,5-Bis(methylthio)isothiazole-4-carboxylic acid **46w** (27.0 mg, 0.122 mmol), 6-aminoflavone **5g** (37.6 mg, 0.122 mmol), HBTU (60.3 mg, 0.159 mmol, 1.3 equiv), DIPEA (42.5 μL, 0.244 mmol, 2 equiv), DMF (2 mL). Solvent for extraction: ethyl acetate and water containing 50% brine. Chromatography on silica gel gave compound **SI103** (6.7 mg, 0.015 mmol, 12%) as a yellow solid. M.p. 245.3–270.7 °C (decomp.). ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.40 (s, 1H), 8.42 (d, 1H, ^{4}J = 2.7 Hz), 8.15–8.09 (m, 2H), 8.06 (dd, 1H, ^{3}J = 9.1 Hz, ^{4}J = 2.7 Hz), 7.82 (d, 1H, ^{3}J = 9.1 Hz), 7.66–7.56 (m, 3H), 7.03 (s, 1H), 2.68 (s, 3H), 2.58 (s, 3H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 176.8, 169.6, 163.2, 162.4, 160.3, 152.2, 136.1, 131.7, 131.1, 129.1, 126.4, 126.3, 123.5, 119.1, 114.2, 112.7, 106.5, 18.4, 12.1, 11.9 ppm. HRMS calc. for $C_{21}H_{17}N_2O_3S_3$ $[M+H]^+$: 441.0401, found 441.0401.

_N_-(4-Oxo-2-phenyl-4_H_-chromen-6-yl)-4-phenyl-1,2,3-thiadiazole-5-carboxamide (SI104)



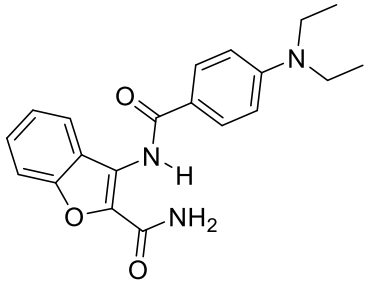
Synthesis according to the General procedure I. 4-Phenyl-1,2,3-thiadiazole-5-carboxylic acid **46n** (31.9 mg, 0.158 mmol), 6-aminoflavone **5g** (34.1 mg, 0.158 mmol), HBTU (71.0 mg, 0.187 mmol, 1.3 equiv), DIPEA (50.2 μL, 0.288 mmol, 2 equiv), DMF (1 mL). Solvent for extraction: ethyl acetate and a mixture of water and brine (1:1). Chromatography on silica gel gave compound **SI104** (33.8 mg, 0.0794 mmol, 55%) as a yellow solid. M.p. 222.2–223.9 °C (decomp.). ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.29 (s, 1H), 8.42 (d, 1H, ^{4}J = 2.6 Hz), 8.15–8.07 (m, 2H), 7.99–7.89 (m, 3H), 7.83 (d, 1H, ^{3}J = 9.1 Hz), 7.66–7.47 (m, 6H), 7.05 (s, 1H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 176.7, 162.5, 159.1, 158.3, 152.4, 144.2, 135.5, 131.8, 131.0, 129.9, 129.7, 129.1, 129.0, 128.2, 126.3, 123.5, 119.4, 114.5, 106.5 ppm. HRMS calc. for $C_{24}H_{16}N_3O_3S$ $[M+H]^+$: 426.0912, found 426.0913.

3-Methyl-_N_-(4-oxo-2-phenyl-4_H_-chromen-6-yl)-5-phenylisoxazole-4-carboxamide (SI105)



Synthesis according to the General procedure I. Deviating from the General procedure I, the reaction time was 4 d. 3-Methyl-5-phenyl-isoxazole-4-carboxylic acid (105 mg, 0.516 mmol), 6-aminoflavone **5g** (122 mg, 0.515 mmol), HBTU (254 mg, 0.671 mmol, 1.3 equiv), DIPEA (0.180 mL, 1.03 mmol, 2 equiv), DMF (3 mL). Solvent for extraction: ethyl acetate/diethyl ether (1:1) and water containing 30% brine. Chromatography on silica gel gave compound **SI105** (162 mg, 0.383 mmol, 74%) as slightly yellow crystals. M.p. 215.2–217.8 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.86 (s, 1H), 8.46 (d, 1H, J = 2.7 Hz), 8.16–8.08 (m, 2H), 8.00 (dd, 1H, J = 2.7 Hz, J = 9.1 Hz), 7.87–7.79 (m, 3H), 7.66–7.52 (m, 6H), 7.05 (s, 1H), 2.41 (s, 3H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 176.8, 166.5, 162.4, 160.3, 159.0, 152.1, 135.9, 131.8, 131.1, 131.0, 129.2, 129.1, 126.8, 126.3, 126.3, 126.2, 123.5, 119.3, 114.2, 113.0, 106.5, 10.2 ppm. HRMS calc. for $C_{26}H_{19}N_2O_4$ $[M+H]^+$: 423.1345, found 423.1346.

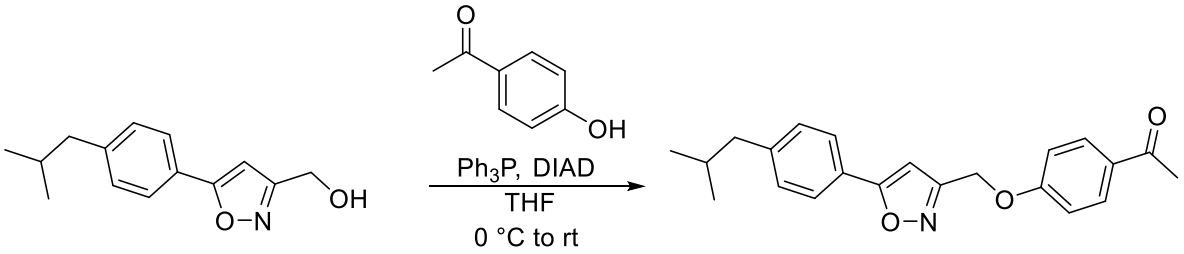
3-[4-(Diethylamino)benzamido]benzofuran-2-carboxamide (SI106)



Synthesis according to the General procedure II. Deviating from the General procedure II, the oxalyl chloride solution was stirred at room temperature for 1 h, and DIPEA was added to the pyridine solution. 4-(Diethylamino)benzoic acid **29** (387 mg, 2.00 mmol), 3-aminobenzofuran-2-carboxamide (352 mg, 2.00 mmol), a 2 M solution of oxalyl chloride in DCM (4.00 mL, 8.00 mmol, 4 equiv), DMF (16.7 μL, 0.200 mmol, 0.1 equiv), DCM (3 mL), DIPEA (0.522 mL, 3.00 mmol, 1.5 equiv), pyridine (5 mL). Solvent for extraction: ethyl acetate. Recrystallization (MeOH/H_2O 20+1) after chromatography on silica gel gave compound **SI106** (207 mg, 0.589 mmol,

29%) as slightly yellow needles. M.p. 191.3–192.6 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.88 (s, 1H), 8.37 (ddd, 1H, ^{3}J = 8.1 Hz, ^{4}J = 1.4 Hz, ^{5}J = 0.7 Hz), 8.21 (bs, 1H), 7.92 (bs, 1H), 7.81 (m$_c$, 2H), 7.59 (ddd≈dt, 1H, ^{3}J = 8.4 Hz, ^{4}J = 1.3), 7.52 (ddd, 1H, ^{3}J = 7.0 Hz), 7.33 (ddd, 1H), 6.78 (m$_c$, 2H), 3.42 (q, 4H, ^{3}J = 7.0 Hz), 1.13 (t, 6H, ^{3}J = 7.0 Hz) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 163.8, 162.7, 152.7, 150.3, 133.1, 129.3, 127.9, 127.8, 126.2, 122.9, 122.0, 118.4, 111.8, 110.5, 43.8, 12.4 ppm. HRMS calc. for $C_{20}H_{22}N_3O_3$ [M+H]$^+$: 352.1661 found 352.1667.

1-[4-[[5-(4-Isobutylphenyl)isoxazol-3-yl]methoxy]phenyl]ethanone (SI107)

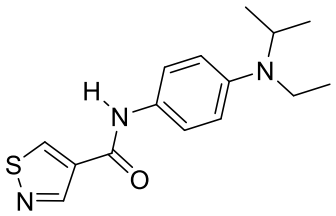


SI107

[5-(4-Isobutylphenyl)isoxazol-3-yl]methanol (0.100 g, 0.432 mmol), 4′-hydroxyacetophenone (70.2 mg, 0.518 mmol, 1.2 equiv) and triphenylphosphine (136 mg, 0.518 mmol, 1.2 equiv) were dissolved in anhydrous THF (2 mL) under argon and cooled to 0 °C in an ice bath. Diisopropyl azodicarboxylate (0.102 mL, 0.518 mmol, 1.2 equiv) was added, and the reaction mixture was stirred for 1 h at 0 °C and overnight at room temperature. Ethyl acetate was added, and the organic phase was washed three times with water. The solvent was removed with a rotary evaporator, and the crude product was purified by automated chromatography on silica gel, using a gradient of increasing ethyl acetate starting with 100% *n*-hexane to give compound **SI107** (128 mg, 0.366 mmol, 85%) as white crystals. M.p. 109.7–110.3 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.96 (m$_c$, 2H), 7.79 (m$_c$, 2H), 7.32 (m$_c$, 2H), 7.19 (m$_c$, 2H), 7.09 (s, 1H), 5.35 (s, 2H), 2.52 (s, 3H), 2.51 (d, 2H, ^{3}J = 6.7 Hz), 1.87 (dsept≈sept, 1H, ^{3}J = Hz), 0.87 (d, 6H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 196.2, 169.7, 161.5, 160.8, 144.0, 130.5, 130.4, 129.7, 125.4, 124.2, 114.6, 99.3, 61.4, 44.3, 29.4, 26.4, 22.0 ppm. HRMS calc. for $C_{22}H_{24}NO_3$M+H]$^+$: 350.1758, found 350.1756.

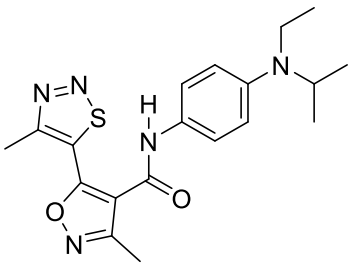
Synthesis of compounds in Tables 6-8 (compounds not included in Schemes 1-4 and Table 1)

***N*-[4-[Ethyl(isopropyl)amino]phenyl]isothiazole-4-carboxamide (61)**



Synthesis according to the General procedure I. Isothiazole-4-carboxylic acid **46s** (0.100 g, 0.774 mmol), *N*-ethyl-*N*-isopropylphenylenediamine hydrochloride (166 mg, 0.773 mmol), HBTU (381 mg, 1.01 mmol, 1.3 equiv), DIPEA (0.404 mL, 2.32 mmol, 3 equiv), DMF (1.5 mL). Solvent for extraction: ethyl acetate and water containing 50% brine. Chromatography on silica gel gave compound **61** (184 mg, 0.636 mmol, 82%) as a yellowish oil. ^{1}H NMR (300 MHz, Acetone-d_6): δ 9.38 (br s, 1H), 9.11 (d, 1H, ^{4}J = 2.1 Hz), 8.31 (d, 1H, ^{4}J = 2.1 Hz), 7.69 (m$_c$, 2H), 6.79 (m$_c$, 2H), 4.05 (sep, 1H, ^{3}J = 6.6 Hz), 3.27 (q, 2H, ^{3}J = 7.0 Hz), 1.18 (d, 6H, ^{3}J = 6.6 Hz), 1.14 (t, 3H, ^{3}J = 7.0 Hz) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 158.3, 154.7, 151.1, 144.9, 127.4, 124.4, 121.9, 112.9, 47.9, 37.4, 19.7, 14.8 ppm. HRMS calc. for $C_{15}H_{20}N_3OS$ [M+H]$^+$: 290.1327, found 290.1334.

***N*-[4-[Ethyl(isopropyl)amino]phenyl]-3-methyl-5-(4-methyl-1,2,3-thiadiazol-5-yl)isoxazole-4-carboxamide (62)**

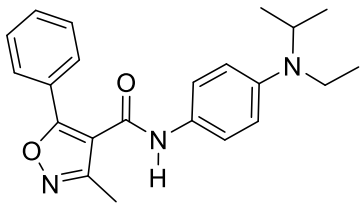


Synthesis according to the General procedure I. Deviating from the General procedure I, the reaction time was 4 d and the coupling reagent 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate (HATU) was used instead of HBTU. 3-Methyl-5-(4-methyl-1,2,3-thiadiazol-5-yl)isoxazole-4-carboxylic acid **46c** (25.5 mg, 0.113 mmol), *N*-ethyl-*N*-isopropylphenylenediamine hydrochloride (24.3 mg, 0.113 mmol), HATU (55.9 mg, 0.147 mmol, 1.3 equiv), DIPEA (59.0 µL, 0.339 mmol, 2 equiv), DMF (1 mL). Solvent for extraction: diethyl ether and a mixture of water and brine (4:1). Chromatography on silica gel gave compound **SI-107** (42.0 mg, 0.109 mmol, 96%) as an orange resin. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.13 (s, 1H), 7.41 (m$_c$, 2H), 6.73 (m$_c$, 2H), 4.00 (sep, 1H, J = 6.6 Hz), 3.20 (q, 2H, J = 6.9 Hz), 2.89 (s, 3H), 2.47 (s, 3H), 1.12 (d, 6H, J = 6.6 Hz), 1.08 (t, 3H, J = 6.9 Hz) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 158.9, 158.5, 158.0, 157.8, 145.4, 134.2, 126.7, 121.7, 117.6, 112.7, 47.9, 37.3, 19.7, 14.7, 14.0, 10.4 ppm. HRMS calc. for $C_{19}H_{24}N_5O_2S$ [M+H]$^+$: 386.1651, found 386.1651.

***N*-[4-[Ethyl(isopropyl)amino]phenyl]-3-methyl-5-phenylisoxazole-4-carboxamide (63)**

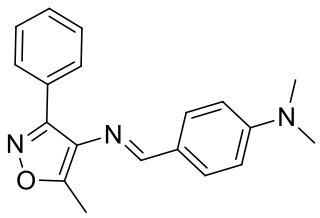
Synthesis according to the General procedure I. 3-Methyl-5-phenylisoxazole-4-carboxylic acid (102 mg, 0.500 mmol), *N*-ethyl-*N*-isopropylphenylenediamine hydrochloride (107 mg, 0.500 mmol), HBTU (247 mg, 0.650 mmol, 1.3 equiv), DIPEA (0.261 mL, 0.261 mmol, 3 equiv), DMF (1.5 mL). Solvent for extraction: diethyl ether. Chromatography on silica gel gave compound **63** (145 mg, 0.451

mmol, 90%) as yellow needles. M.p. 133.9–135.2 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.19 (s, 1H), 7.85–7.70 (m, 2H), 7.59–7.50 (m, 3H), 7.44 (m_c, 2H), 6.72 (m_c, 2H), 3.98 (sept, 1H, ^{3}J = 6.6 Hz), 3.20 (q, 2H, ^{3}J = 7.0 Hz), 2.35 (s, 3H), 1.12 (d, 6H, ^{3}J = 6.6 Hz), 1.07 (t, 3H, ^{3}J = 7.0 Hz) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 165.5, 159.1, 158.9, 145.1, 130.7, 129.1, 127.5, 126.5, 126.5, 121.3, 113.7, 113.0, 48.0, 37.3, 19.7, 14.7, 10.1 ppm. HRMS calc. for $C_{22}H_{26}N_3O_2$ $[M+H]^+$: 364.2025, found 364.2026.

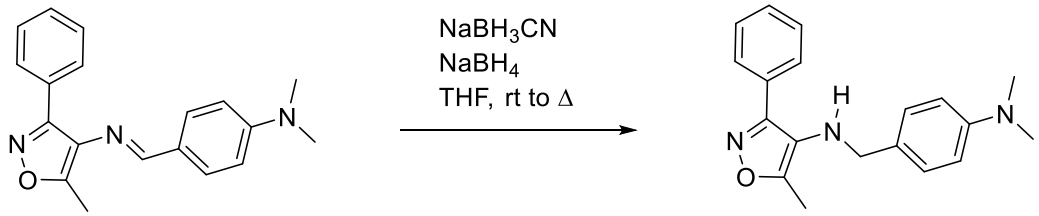


(*E*)-*N*-4-[(Dimethylamino)benzylidene]-5-methyl-3-phenylisoxazol-4-amine (SI108)

Synthesis according to the General procedure III. Deviating from the General procedure III, reaction mixture was heated at 100 °C for 9 h. 4-(Dimethylamino)benzaldehyde, (214 mg, 1.43 mmol), 5-methyl-3-phenylisoxazol-4-amine **28** (0.250 g, 1.43 mmol), Na_2SO_4 (509 mg, 3.58 mmol, 2.5 equiv), AcOH (20.5 μL, 0.358 mmol, 0.25 equiv), toluene (2.5 mL). Recrystallization (ethyl acetate) after chromatography on silica gel gave compound **SI108** (142 mg, 0.465 mmol, 32%) as yellowish crystals. M.p. 155.2–158.6 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.40 (s, 1H), 7.95–7.87 (m, 2H), 7.72 (m_c, 2H), 7.52–7.45 (m, 3H), 6.80 (m_c, 2H), 3.01 (s, 6H), 2.48 (s, 3H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 163.3, 156.7, 156.4, 152.6, 130.0, 129.5, 128.9, 128.6, 128.5, 127.5, 123.4, 111.5, 39.6, 11.1 ppm. HRMS calc. for $C_{19}H_{20}N_3O$ $[M+H]^+$: 306.1606, found 306.1608.



_N_-4-[(Dimethylamino)benzyl]-5-methyl-3-phenylisoxazol-4-amine (SI109)

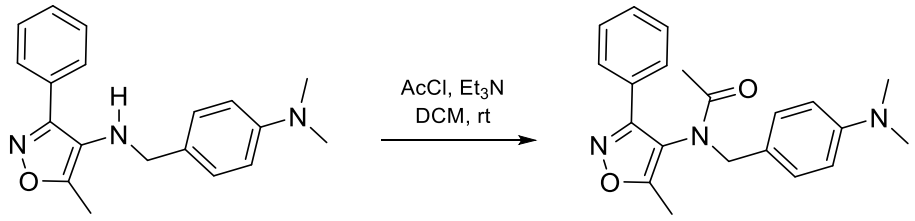


SI108 **SI109**

(*E*)-*N*-[4-(Dimethylamino)benzylidene]-5-methyl-3-phenylisoxazol-4-amine **SI108** (90.0 mg, 0.295 mmol) was dissolved in absolute methanol (1 mL) under argon. Sodium cyanoborohydride (22.2 mg, 0.354 mmol) was added, and the reaction mixture was stirred overnight at room temperature. THF (1 mL) was added, and stirring was continued overnight. The second portion of *sodium cyanoborohydride* (11.1 mg, 0.177 mmol) was added, and the reaction mixture was heated at 40 °C for 3 d. The third portion of sodium cyanoborohydride (44.4 mg, 0.708 mmol) was added and stirring at 40 °C was continued for 2 d. Then *sodium borohydride* (12.3 mg, 0.325 mmol) was added and heating was continued for 2 d. The second portion of *sodium borohydride* (12.3 mg, 0.325 mmol) was added, and heating was continued for 4 d. First, a small amount of water was added, and after 15

min ethyl acetate and water were added. The phases were separated and the organic phase was washed twice with water. The solvent was removed with a rotary evaporator and the crude product was purified by automated preparative chromatography. The chromatography on silica gel was performed with an increasing gradient of ethyl acetate in *n*-hexane, starting with 0% of ethyl acetate to give compound **SI109** (41.0 mg, 0.133 mmol, 45%) as a colorless oil. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.93–7.84 (m, 2H), 7.55–7.45 (m, 3H), 6.97 (m$_c$, 2H), 6.61 (m$_c$, 2H), 4.30 (t, 1H, ^{3}J = 6.9 Hz), 3.72 (d, 2H), 2.84 (s, 6H), 2.16 (s, 3H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ159.1, 157.3, 149.5 , 129.4, 129.3, 128.7, 128.6, 127.3, 127.0, 123.1, 112.1, 51.4, 40.1, 10.1 ppm. HRMS calc. for $C_{19}H_{22}N_3O$ $[M+H]^+$: 308.1763, found 308.1768.

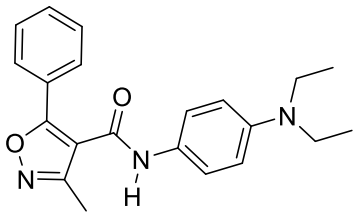
_N_-[4-(Dimethylamino)benzyl]-_N_-(5-methyl-3-phenylisoxazol-4-yl)acetamide (64)



SI109 **64**

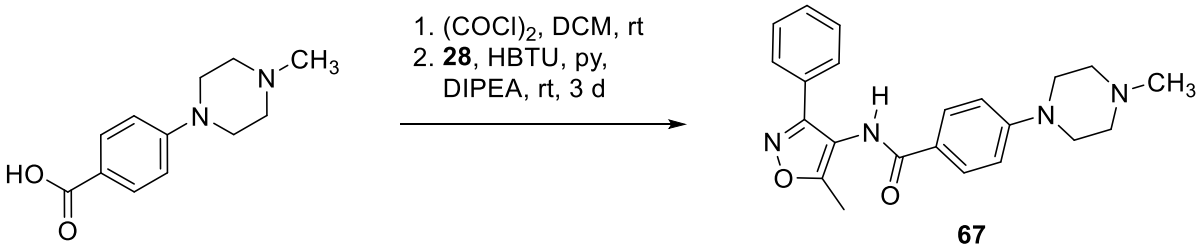
To a solution of *N*-[4-(dimethylamino)benzyl]-5-methyl-3-phenylisoxazol-4-amine **SI109** (26.0 mg, 0.0846 mmol) and triethylamine (29.5 µL, 0.212 mmol, 2.5 equiv) in absolute DCM (0.3 mL) was added acetyl chloride (9.0 µL, 0.13 mmol, 1.5 equiv) under argon. The reaction mixture was stirred for 1 h at room temperature. Triethylamine (29.5 µL, 0.212 mmol, 2.5 equiv) and acetyl chloride (9.0 µL, 0.13 mmol, 1.5 equiv) were added and stirring was continued overnight. Finally, DCM (0.5 mL), triethylamine (89 µL, 0.64 mmol, 7.5 equiv) and acetyl chloride (27 µL, 0.38 mmol, 4.5 equiv) were added and stirring was continued for 2 h. A 5% solution of sodium hydrogen carbonate in water and ethyl acetate were added, the phases were separated, and the organic phase was washed twice with water. The organic solvent was removed with a rotary evaporator, and the crude product was purified by automated preparative chromatography. The chromatography on silica gel was performed with an increasing gradient of ethyl acetate in *n*-hexane, starting with 0% of ethyl acetate gave compound **64** (11.8 mg, 33.8 µmol, 40%) as a colorless oil. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.62–7.44 (m, 5H), 6.93 (m$_c$, 2H), 6.58 (m$_c$, 2H), 5.17 (d, 1H, ^{3}J = 13.7 Hz), 3.73 (d, 1H), 2.84 (s, 6H), 1.83 (s, 3H), 1.81 (s, 3H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ170.0, 167.6, 158.0, 150.0, 130.4, 130.2, 129.3, 127.5, 126.6, 123.8, 117.3, 112.0, 49.9, 40.1, 21.9, 10.0 ppm. HRMS calc. for $C_{21}H_{24}N_3O_2$ $[M+H]^+$: 350.1869, found 350.1869.

N-[4-(Diethylamino)phenyl]-3-methyl-5-phenylisoxazole-4-carboxamide (65)



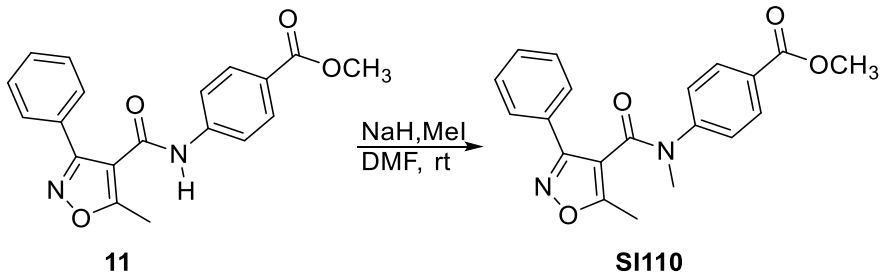
Synthesis according to the General procedure I. 3-Methyl-5-phenyl-4-isoxazolecarboxylic acid (102 mg, 0.500 mmol), *N*,*N*-diethyl-*p*-phenylenediamine **17** (83.1 μL, 0.500 mmol), HBTU (246.5 mg, 0.650 mmol, 1.3 equiv), DIPEA (0.174 mL, 1.00 mmol, 2 equiv), DMF (2 mL). Solvent for extraction: diethyl ether. Recrystallization (MeOH/H_2O 10+1) without chromatography on silica gel gave compound **65** (150 mg, 0.428 mmol, 86%) as yellow needles. M.p. 159.0–160.2 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.18 (s, 1H), 7.85–7.78 (m, 2H), 7.57–7.51 (m, 3H), 7.43 (m$_c$, 2H), 6.65 (m$_c$, 2H), 3.31 (q, 4H, J = 7.0 Hz), 2.35 (s, 3H), 1.07 (t, 6H, J = 7.0 Hz) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 165.5, 159.0, 158.9, 144.6, 130.7, 129.1, 127.1, 126.5, 126.5, 121.5, 113.8, 111.8, 43.7, 12.3, 10.1 ppm. HRMS calc. for $C_{21}H_{24}N_3O_2$ [M+H]$^+$: 350.1869, found 350.1870.

N-(5-Methyl-3-phenylisoxazol-4-yl)-4-(4-methylpiperazin-1-yl)benzamide (67)



4-(4-Methylpiperazin-1-yl)benzoic acid (75.0 mg, 0.340 mmol) was dissolved in anhydrous dichloromethane (3 mL) under argon. Oxalyl chloride (0.146 mL, 1.70 mmol, 5 equiv) was added, and the reaction mixture was stirred at room temperature for 2 h. The organic solvents were removed with a rotary evaporator, and the residue was dissolved in anhydrous pyridine (2 mL). To this solution, 5-methyl-3-phenylisoxazol-4-amine **28** (59.3 mg, 0.340 mmol) and DIPEA (0.178 mL, 1.02 mmol, 3 equiv) were added, and the resulting mixture was stirred at room temperature overnight. Then HBTU (155 mg, 0.408 mmol, 1.2 equiv) and DIPEA (178 μL, 1.02 mmol, 3 equiv) were added, and the reaction mixture was stirred at room temperature for 3 d. HBTU (77.0 mg, 0.204 mmol, 0.6 equiv) were added and the reaction mixture was heated at 80 °C for 7 h. Ethyl acetate was added and the organic phase was washed three times with a mixture of water and brine (1+1). The automated chromatography on silica gel was performed with an increasing gradient of ethyl acetate in *n*-hexane, starting with 0% of ethyl acetate. Recrystallization (MeOH/H_2O 10+1) gave compound **67** (0.040 g, (0.106 mmol, 31%) as beige needles. M.p. 192.0–194.4 °C (decomp.). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74 (m$_c$, 2H), 7.68–7.61 (m, 2H), 7.44–7.35 (m, 3H), 7.12 (s, 1H), 6.89 (m$_c$, 2H), 3.33 (m$_c$, 4H), 2.55 (m$_c$, 4H), 2.42 (s, 3H), 2.34 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.3, 159.3, 154.0, 130.1, 129.2, 129.1, 128.5, 127.9, 122.6, 114.3, 112.5, 54.9, 47.7, 46.3, 12.1 ppm. HRMS calc. for $C_{22}H_{25}N_4O_2$ [M+H]$^+$: 377.1978, found 377.1974.

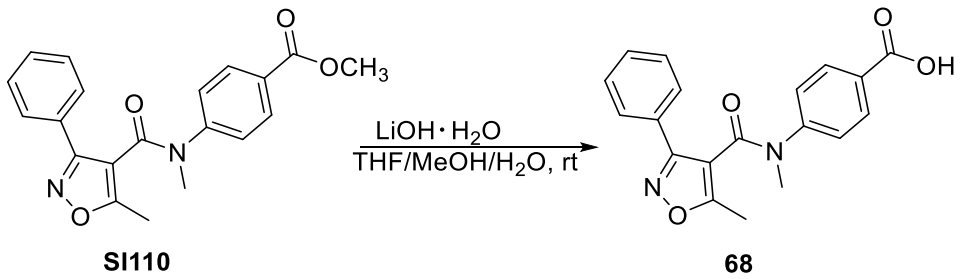
Methyl 4-(*N*,5-dimethyl-3-phenylisoxazole-4-carboxamido)benzoate (SI110)



11 **SI110**

Methyl 4-(5-methyl-3-phenylisoxazole-4-carboxamido)benzoate **11** (183 mg, 0.543 mmol) was dissolved under argon in absolute DMF (4 mL). A 60% suspension of sodium hydride in mineral oil (23.9 mg, 0.597 mmol, 1.1 equiv) was added, and the reaction mixture was stirred for 3 h at room temperature. Iodomethane (50.7 µL, 0.815 mmol, 1.5 equiv) was added, and the reaction mixture was stirred overnight at room temperature. The reaction mixture was diluted with diethyl ether and washed three times with a mixture of water and brine (3:1). The solvent was removed at a rotary evaporator and the residue was subjected to automated preparative chromatography. The chromatography on silica gel was performed with an increasing gradient of ethyl acetate in *n*-hexane, starting with 0% of ethyl acetate gave compound **SI110** (0.180 g, 0.514 mmol, 95%) as a colorless oil. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.76 (m$_c$, 2H), 7.75–7.41 (m, 3H), 7.37–7.31 (m, 2H), 6.92 (m$_c$, 2H), 3.82 (s, 3H), 3.33 (s, 3H), 2.41 (s, 3H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 170.5, 165.9, 162.5, 160.0, 147.1, 130.5, 129.9, 129.4, 128.3, 127.6, 127.5, 126.3, 112.4, 52.6, 37.2, 12.0 ppm. HRMS calc. for $C_{20}H_{19}N_2O_4$ $[M+H]^+$: 351.1345, found 351.1352.

4-(*N*,5-Dimethyl-3-phenylisoxazole-4-carboxamido)benzoic acid (68)

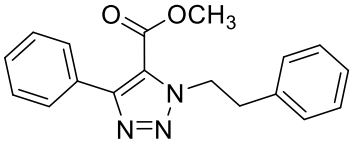


SI110 **68**

Methyl 4-(*N*,5-dimethyl-3-phenylisoxazole-4-carboxamido)benzoate **SI110** (129 mg, 0.368 mmol) was dissolved in an equimixture of THF, MeOH and water (6 mL). Lithium hydroxide hydrate (18.5 mg, 0.442 mmol) was added, and the reaction mixture was stirred overnight at room temperature. Diethyl ether was added and the organic phase was extracted twice with water. The combined aqueous phases were acidified with a 1 M solution of HCl in H_2O and extracted with ethyl acetate. The organic phase was washed four times with water until the aqueous phase remained neutral. Evaporation of the organic phase with a rotary evaporator and drying *in vacuo* gave compound **68** (98.5 mg, 0.293

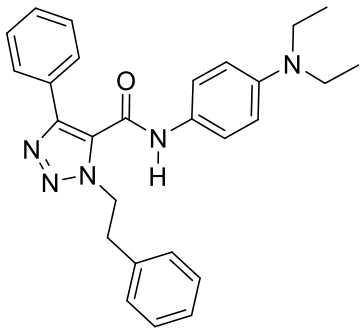
mmol, 80%) as a white solid. M.p. 219.5–220.7 °C. ^{1}H NMR (300 MHz, DMSO-*d*$_6$): δ 12.92 (bs, 1H), 7.63 (m$_c$, 2H), 7.53–7.40 (m, 3H), 7.37–7.30 (m, 2H), 6.88 (m$_c$, 2H), 3.31 (s, 3H), 2.39 (s, 3H) ppm. ^{13}C NMR (75 MHz, DMSO-*d*$_6$): δ 169.8, 166.4, 162.0, 159.5, 146.2, 130.0, 129.6, 128.8, 128.3, 127.8, 127.0, 125.6, 111.9, 36.7, 11.5 ppm. HRMS calc. for $C_{19}H_{17}N_2O_4$ $[M+H]^+$: 337.1188, found 337.1195.

Methyl 1-phenethyl-4-phenyl-1*H*-1,2,3-triazole-5-carboxylate (SI111)



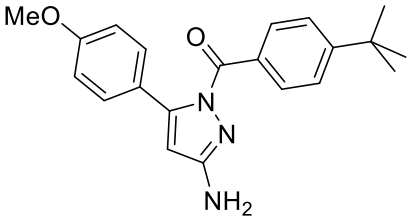
(2-Bromoethyl)benzene (0.137 mL, 1.00 mmol) was dissolved in ethanol (2 mL). Sodium azide (65.0 mg, 1.00 mmol) was added, and the reaction mixture was stirred under reflux conditions overnight. Ethanol was removed with a rotary evaporator. Methyl phenylpropiolate (0.160 g, 1.00 mmol) and toluene (2 mL) were added and the reaction mixture was heated at 110 °C under reflux conditions for 3 d. The reaction mixture was diluted with ethyl acetate and washed three times with water. The organic solvent was removed with a rotary evaporator. The crude product was purified by automated chromatography on silica gel, using a gradient of increasing ethyl acetate starting with 100% *n*-hexane to give compound **SI111** (76.4 mg, 0.249 mmol, 25%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.72–7.65 (m, 2H), 7.47–7.38 (m, 3H), 7.34–7.17 (m, 5H,), 4.96 (m$_c$, 1H), 3.78 (s, 3H), 3.24 (m$_c$, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.8, 150.3, 137.1, 130.5, 129.5, 129.1, 128.9, 128.2, 127.1, 50.4, 50.2, 37.2 ppm. HRMS calc. for $C_{18}H_{18}N_3O_2$ $[M+H]^+$: 308.1399, found 308.1400.

***N*-[4-(Diethylamino)phenyl]-1-phenethyl-4-phenyl-1*H*-1,2,3-triazole-5-carboxamide (71)**

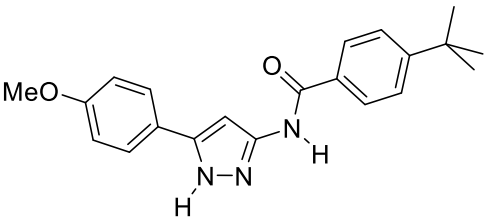


Synthesis according to the General procedure VI. Methyl 1-phenethyl-4-phenyl-1*H*-1,2,3-triazole-5-carboxylate **SI111** (55.1 mg, 0.179 mmol), LiOH·H_2O (11.3 mg, 0.269 mmol, 1.5 equiv), solvent volume: 200 μL each. *N*,*N*-Diethyl-*p*-phenylenediamine **17** (29.8 μL, 0.179 mmol), HBTU (97.1 mg, 0.256 mmol, 1.3 equiv), DIPEA (62.4 μL, 0.358 mmol, 2 equiv), DMF (2 mL). Solvent for extraction: diethyl ether. Chromatography on silica gel gave compound **71** (25.4 mg, 0.0578 mmol, 32%) as a greenish solid. M.p. 138.4–139.8 °C. ^{1}H NMR (300 MHz, DMSO-*d*$_6$): δ 10.58 (s, 1H), 7.79–7.74 (m, 2H), 7.50–7.17 (m, 10H), 6.68 (m$_c$, 2H), 4.70 (t, 1H, ^{3}J = 7.4 Hz), 3.32 (q, 4H, ^{3}J = 7.0 Hz), 3.20 (t, 1H), 1.09 (t, 6H, ^{3}J = 7.0 Hz) ppm. ^{13}C NMR (75 MHz, DMSO-*d*$_6$): δ 157.0, 144.9, 143.4, 137.2, 130.1, 129.8 , 128.8, 128.6, 128.4, 128.3, 126.6, 126.3, 126.3, 121.8, 111.6, 50.1, 43.7, 35.4, 12.3 ppm. HRMS calc. for $C_{27}H_{30}N_5O$ $[M+H]^+$: 440.2450, found 440.2452.

[3-Amino-5-(4-methoxyphenyl)-1*H*-pyrazol-1-yl][4-(*tert*-butyl)phenyl]methanone (SI112) and 4-(*tert*-butyl)-*N*-[5-(4-methoxyphenyl)-1*H*-pyrazol-3-yl]benzamide (72)



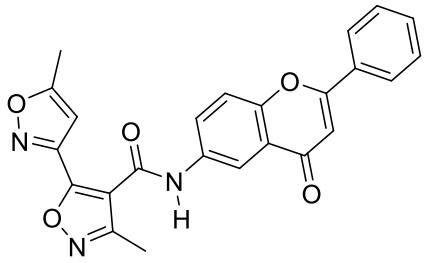
SI112



72

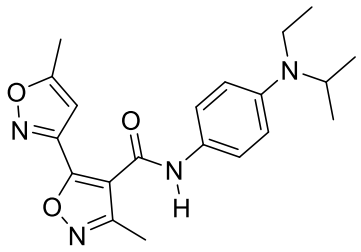
Synthesis according to the General procedure I. 4-(*tert*-Butyl)benzoic acid (178 mg, 1.00 mmol), 5-(4-methoxyphenyl)-1*H*-pyrazol-3-amine (189 mg, 1.00 mmol), HBTU (493 mg, 1.30 mmol, 1.3 equiv), DIPEA (0.348 mL, 2.00 mmol, 2 equiv), DMF (3 mL). Solvent for extraction: ethyl acetate. Automated chromatography on silica gel and subsequent recrystallization (EtOH/H_2O 19+1) gave compound **SI112** (217 mg, 0.621 mmol, 62%) as white plates and compound **72** (13.0 mg, 0.037 mmol, 4%) as a white solid. Compound **SI112**: M.p. 142.0–143.6 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.07 (m$_c$, 2H), 7.70 (m$_c$, 2H), 7.57 (m$_c$, 2H), 6.98 (m$_c$, 2H), 6.78 (s, 2H), 5.83 (s, 1H), 3.78 (s, 3H), 1.34 (s, 9H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 168.9, 159.9, 155.3, 153.8, 153.0, 130.9, 130.3, 127.3, 124.6, 124.6, 114.0, 84.5, 55.1, 34.7, 30.8 ppm. HRMS calc. for $C_{21}H_{24}N_3O_2$ $[M+H]^+$: 350.1869, found 350.1873. Compound **72**: M.p. 232.1–232.4 °C. ^{1}H NMR (300 MHz, Acetone-d_6): δ 11.87 (br s, 1H), 9.85 (s, 1H), 8.04 (m$_c$, 2H), 7.73 (m$_c$, 2H), 7.57 (m$_c$, 2H), 7.02 (m$_c$, 2H), 6.94 (br s, 1H), 3.85 (s, 3H), 1.36 (s, 9H) ppm. ^{13}C NMR (75 MHz, Acetone-d_6): δ 165.2, 160.7, 155.9, 148.0, 145.1, 132.5, 128.3, 127.5, 126.2, 124.5, 115.2, 93.7, 55.7, 35.5, 31.4 ppm. HRMS calc. for $C_{21}H_{24}N_3O_2$ $[M+H]^+$: 350.1869, found 350.1875.

3',5-Dimethyl-*N*-(4-oxo-2-phenyl-4*H*-chromen-6-yl)-[3,5'-biisoxazole]-4'-carboxamide (73)



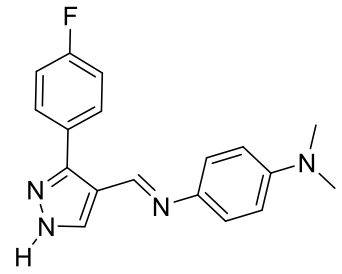
Synthesis according to the General procedure I. Deviating from the General procedure I, HATU was used as coupling reagent and due to the poor solubility of the product a different work-up procedure was used after stirring the reaction mixture overnight. MeOH (2 mL) was added and the suspension was filtered, washed with water and MeOH and dried *in vacuo*. 3-Methyl-5-(5-methylisoxazol-3-yl)isoxazole-4-carboxylic acid (40.8 mg, 0.196 mmol), 6-aminoflavone **5g** (46.5 mg, 0.196 mmol), HATU (96.9 mg, 0.155 mmol, 1.3 equiv), DIPEA (68.3 μL, 0.392 mmol, 2 equiv), DMF (2 mL). Filtration gave compound **73** (66.4 mg, 0.0817 mmol, 61%) as a white solid. M.p. 274.4–277.6 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.16 (s, 1H), 8.37 (d, 1H, ^4J = 2.7 Hz), 8.20 (dd, 1H, ^3J = 9.1 Hz), 8.02–7.94 (m, 2H), 7.64 (d, 1H), 7.60–7.51 (m, 3H), 6.80 (s, 1H), 6.69 (q, 1H, ^4J = 0.9 Hz), 2.67 (s, 3H), 2.62 (d, 3H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 177.5, 172.1, 163.2, 163.0, 158.4, 156.4, 153.6, 152.9, 135.8, 131.9, 131.5, 129.0, 126.4, 126.2, 124.3, 118.8, 115.1, 113.9, 107.0, 101.7, 12.1 ppm. HRMS calc. for $C_{24}H_{18}N_3O_5$ $[M+H]^+$: 428.1246, found 428.1249.

_N_-[4-(Ethyl(isopropyl)amino)phenyl]-3',5-dimethyl-[3,5'-biisoxazole]-4'-carboxamide (74)



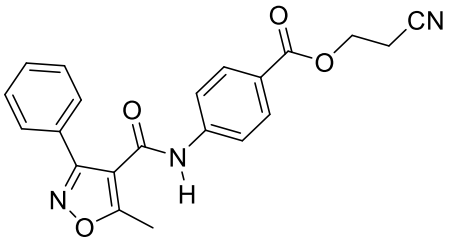
Synthesis according to the General procedure I. Deviating from the General procedure I, HATU was used as coupling reagent. 3-Methyl-5-(5-methylisoxazol-3-yl)isoxazole-4-carboxylic acid (28.5 mg, 0.137 mmol), *N*-ethyl-*N*-isopropylphenylenediamine hydrochloride (29.4 mg, 0.137 mmol), HATU (67.7 mg, 0.178 mmol, 1.3 equiv), DIPEA (71.6 μL, 0.411 mmol, 3 equiv), DMF (2 mL). Solvent for extraction: diethyl ether. Recrystallization ($MeOH/H_2O$ 10+1) without chromatography on silica gel gave compound **74** (30.1 mg, 0.0817 mmol, 60%) as fine yellow needles. M.p. 111.2–114.5 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.22 (s, 1H), 7.44 (m$_c$, 2H), 6.76–6.69 (m, 3H), 3.98 (sept, 1H, ^3J = 6.0 Hz), 3.20 (q, 4H, ^3J = 7.0 Hz), 2.51 (d, 3H, ^4J = 0.9 Hz), 2.40 (s, 3H), 1.12 (d, 6H, ^3J = 6.0 Hz), 1.08 (t, 6H, ^3J = 7.0 Hz) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 171.5, 159.4, 157.4, 156.7, 151.8, 145.2 , 127.4, 121.3, 116.5, 113.0, 101.0, 48.0, 37.3, 19.7, 14.7, 11.7, 10.2 ppm. HRMS calc. for $C_{20}H_{25}N_4O_3$ $[M+H]^+$: 369.1927, found 369.1927.

(*E*)-N^1-[[3-(4-Fluorophenyl)-1*H*-pyrazol-4-yl]methylene]-N^4,N^4-dimethylbenzene-1,4-diamine (75)



Synthesis according to the General procedure III. Deviating from the General procedure III, no acid catalyst was added, and the reaction mixture was heated at 70 °C overnight. 3-(4-Fluorophenyl)-1*H*-pyrazole-4-carbaldehyde (0.190 g, 1.00 mmol), *N*,*N*-dimethyl-*p*-phenylenediamine **42** (136 mg, 1 equiv), Na_2SO_4 (0.200 g, 1.41 mmol), toluene (3 mL). Recrystallization (hexane/benzene 1+1) after chromatography on silica gel gave compound **75** (241 mg, 0.782 mmol, 78%) as a yellow solid. M.p. 100.6–108.3 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 13.39 (bs, 1H), 8.47 (s, 1H), 8.20 (bs, 1H), 7.78 (m$_c$, 2H), 7.34 (m$_c$, 2H), 7.12 (m$_c$, 2H), 6.72 (m$_c$, 2H), 2.89 (s, 6H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 162.1 (d, J = 245.6 Hz), 148.9, 148.3, 141.1, 130.5 (d, J = 8.2 Hz), 128.2, 121.6, 117.4, 115.6 (d, J = 21.3 Hz), 112.8, 40.3 ppm. HRMS calc. for $C_{18}H_{18}FN_4$ $[M+H]^+$: 309.1515, found 309.1515.

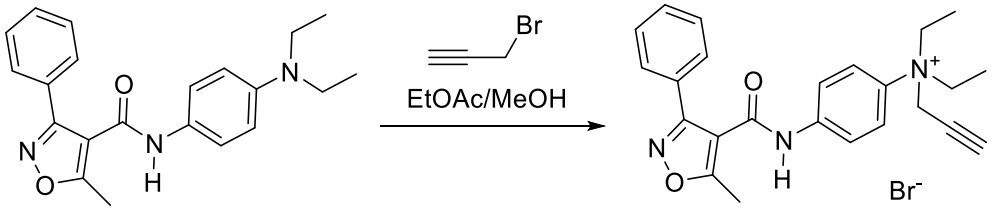
2-Cyanoethyl 4-(5-methyl-3-phenylisoxazole-4-carboxamido)benzoate (76)



Synthesis according to the General procedure VII. Deviating from the General procedure VII, the product was recrystallized from MeOH after chromatography. 4-(5-Methyl-3-phenylisoxazole-4-carboxamido)benzoic acid **12** (39.4 mg, 0.122 mmol), 3-hydroxypropionitrile (25.1 μL, 0.367 mmol, 3 equiv), HBTU (60.1 mg, 0.159 mmol, 1.3 equiv), DIPEA (42.5 μL, 0.244 mmol, 2 equiv), DMF (1 mL). Reaction time: overnight. Solvent for extraction: diethyl ether and water. Recrystallization gave compound **76** (28.6 mg, 0.0762 mmol, 62%) as white crystals.

M.p. 156.3–157.2 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.74 (s, 1H), 7.96 (m$_c$, 2H), 7.77 (m$_c$, 2H), 7.70–7.62 (m, 2H), 7.52–7.43 (m, 3H), 4.43 (t, 2H, ^{3}J = 6.0 Hz), 3.01 (t, 2H, ^{3}J = 6.0 Hz), 2.58 (s, 3H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 170.3, 164.7, 160.4, 160.2, 143.2, 130.4, 130.1, 128.8, 127.9, 127.7, 124.2, 119.2, 118.4, 112.9, 59.5, 17.5, 11.9 ppm. HRMS calc. for $C_{21}H_{18}N_3O_4$ $[M+H]^+$: 376.1297, found 376.1298.

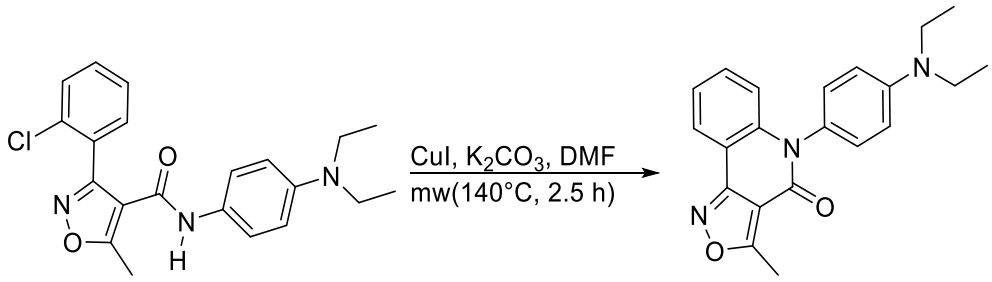
_N_,_N_-Diethyl-4-(5-methyl-3-phenylisoxazole-4-carboxamido)-_N_-(prop-2-yn-1-yl)benzen-aminium bromide (77)



1 **77**

_N_-[4-(Dimethylamino)phenyl]-5-methyl-3-phenylisoxazole-4-carboxamide **1** (0.200 g, 0.572 mmol) was dissolved in a mixture of methanol (3 mL) and ethyl acetate (2 mL). An 80% solution of propargyl bromide in toluene (0.127 mL, 1.14 mmol, 2 equiv) was added, and the reaction mixture was stirred at room temperature for 4 d. Then the reaction mixture was heated at 70 °C overnight. An 80% solution of propargyl bromide in toluene (0.255 mL, 2.29 mmol) was added, and the reaction mixture was heated at 70 °C for 40 h. The organic solvents were evaporated with a rotary evaporator. Diethyl ether and water were added. The aqueous phase was separated and washed once with diethyl ether. Evaporation of the aqueous phase with a rotary evaporator gave compound **77** (154 mg, 0.329 mmol, 58%) as pink crystals. M.p. 162.9–165.1 °C (decomp.). ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.81 (s, 1H), 7.91–7.82 (m, 4H), 7.72–7.65 (m, 2H), 7.54–7.45 (m, 3H), 4.98 (d, 2H, J = 2.5 Hz, C$\underline{H}_2$CCH), 3.99 (t, 1H), 3.97 (q, 4H, ^{3}J = 7.0 Hz), 2.61 (s, 3H), 1.09 (t, 6H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 170.3, 160.4, 160.2, 139.8, 135.8, 130.1, 128.8, 127.8, 127.7, 123.2, 120.3, 112.8, 82.9, 72.2, 58.6, 49.2, 12.0, 8.0, ppm. HRMS calc. for the cation $C_{24}H_{26}N_3O_2^+$ $[M]^+$: 388.2025, found 388.2026.

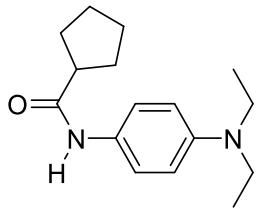
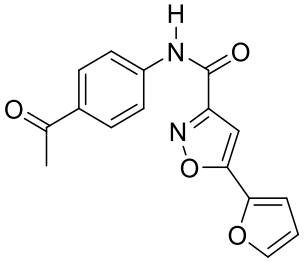
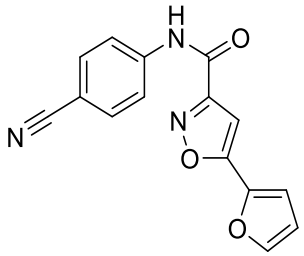
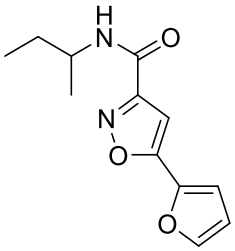
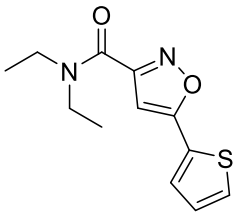
5-[4-(Diethylamino)phenyl]-3-methylisoxazolo[4,3-*c*]quinolin-4(5*H*)-one (78)

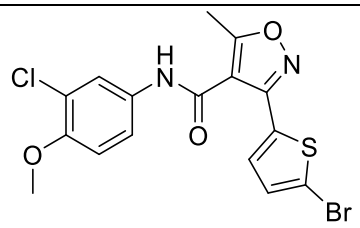
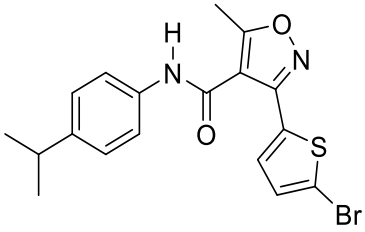
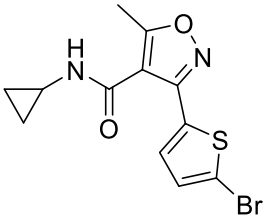
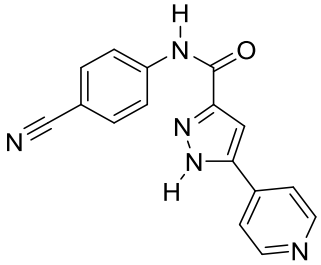
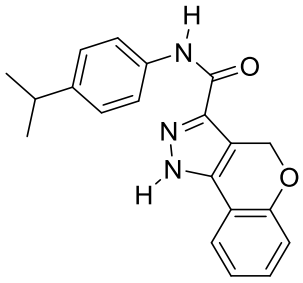


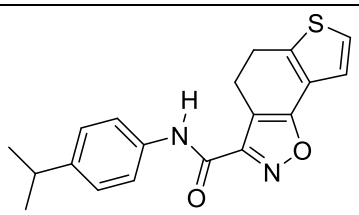
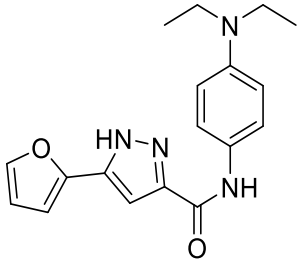
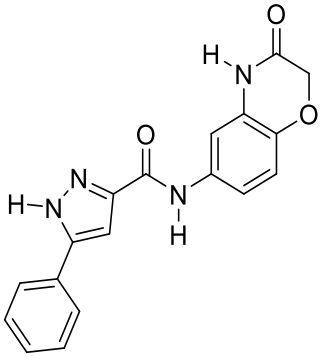
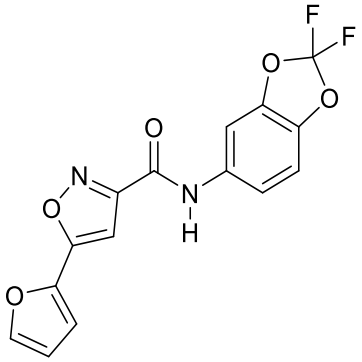
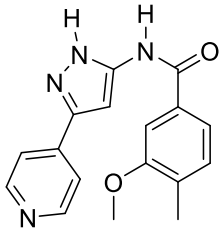
39k **78**

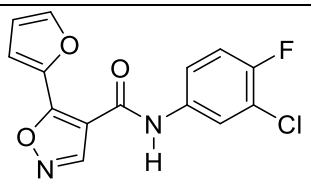
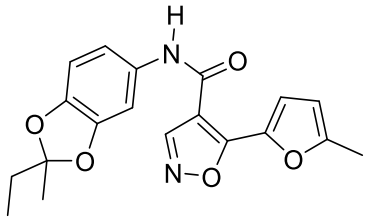
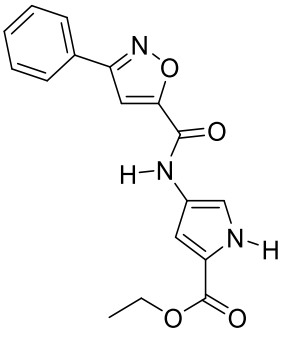
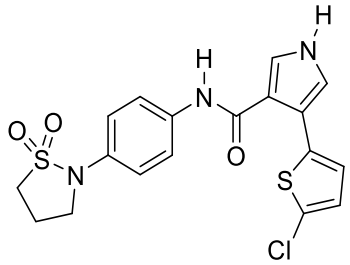
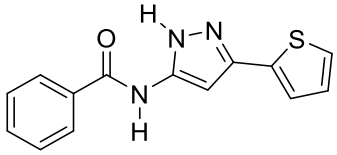
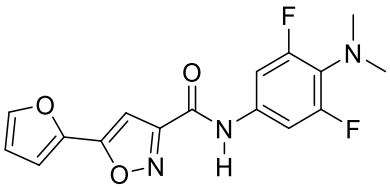
3-(2-Chlorophenyl)-*N*-[4-(diethylamino)phenyl]-5-methylisoxazole-4-carboxamide **39k** (51.0 mg, 0.131 mmol) was dissolved under argon in absolute DMF (1 mL) and the solution was degassed. Copper(I) iodide (25.0 mg, 0.131 mmol) and potassium carbonate (18.1 mg, 0.131 mmol) were added under argon. The reaction mixture was irradiated in a microwave reactor to 140 °C for 2.5 h. DCM was added, and the organic phase was washed twice with water. The solvent was removed with a rotary evaporator, and the crude product was subjected to automated preparative chromatography. The chromatography on silica gel was performed with an increasing gradient of ethyl acetate in *n*-hexane, starting with 0% of ethyl acetate gave compound **78** (5.70 mg, 0.0164 mmol, 13%) as a white solid. M.p. 225.3–227.2 °C. ^{1}H NMR (300 MHz, CD_2Cl_2): δ 8.16 (ddd, 1H, ^{4}J = 0.5 Hz, ^{4}J = 1.7 Hz, ^{3}J = 7.8 Hz), 7.37 (ddd, 1H, ^{4}J = 1.7 Hz, ^{3}J = 7.3 Hz, ^{3}J = 8.8 Hz), 7.21 (ddd, 1H, ^{4}J = 1.2 Hz, ^{3}J = 7.3 Hz, ^{3}J = 7.8 Hz), 7.03 (m_c, 2H), 6.82 (m_c, 2H), 6.75 (m_c, 1H), 3.44 (q, 4H, ^{3}J = 7.1 Hz), 2.86 (s, 3H), 1.23 (t, 6H, 7.1 Hz) ppm. ^{13}C NMR (75 MHz, CD_2Cl_2): δ 175.1, 159.6, 157.3, 148.5, 143.3, 131.9, 130.4, 125.0, 124.7, 123.2, 118.4, 112.8, 112.4, 108.2, 45.1, 13.2, 12.9 ppm. HRMS calc. for $C_{21}H_{22}N_3O_2$ $[M+H]^+$: 348.1712, found 348.1715.

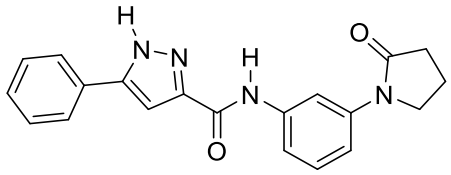
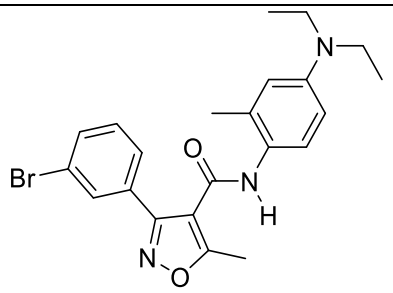
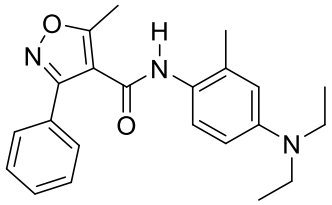
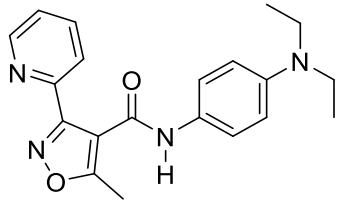
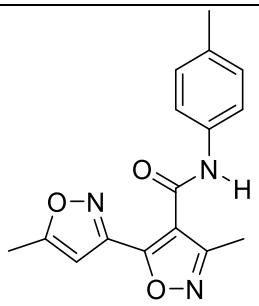
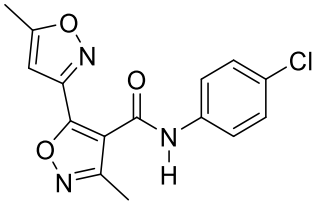
Table S1. List of commercial compounds and suppliers

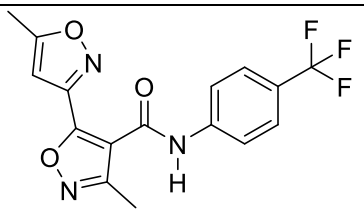
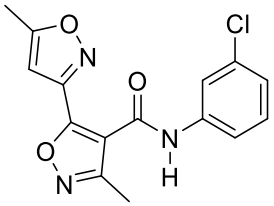
Structure	Cmpd	Supplier	Supplier id
 *N*-[4-(diethylamino)phenyl]cyclopentanecarboxamide	**57**	ChemBridge	7264871
 *N*-(4-acetylphenyl)-5-(furan-2-yl)isoxazole-3-carboxamide	**70**	ChemBridge	9249938
 *N*-(4-cyanophenyl)-5-(furan-2-yl)isoxazole-3-carboxamide	**SI113**	ChemBridge	9265701
 *N*-(*sec*-butyl)-5-(furan-2-yl)isoxazole-3-carboxamide	**69**	ChemDiv	C226-1747
 *N*,*N*-diethyl-5-(thiophen-2-yl)isoxazole-3-carboxamide	**SI114**	ChemDiv	C226-1870

 3-(5-bromothiophen-2-yl)-*N*-(3-chloro-4-methoxyphenyl)-5-methylisoxazole-4-carboxamide	**SI115**	ChemDiv	F082-0953
 3-(5-bromothiophen-2-yl)-*N*-(4-isopropylphenyl)-5-methylisoxazole-4-carboxamide	**SI116**	ChemDiv	F082-0919
 3-(5-bromothiophen-2-yl)-*N*-cyclopropyl-5-methylisoxazole-4-carboxamide	**SI117**	ChemDiv	F082-0893
 *N*-(4-cyanophenyl)-5-(pyridin-4-yl)-1*H*-pyrazole-3-carboxamide	**SI118**	ChemDiv	G639-0128
 *N*-(4-isopropylphenyl)-1,4-dihydrochromeno[4,3-*c*]pyrazole-3-carboxamide	**SI119**	ChemDiv	G365-0453

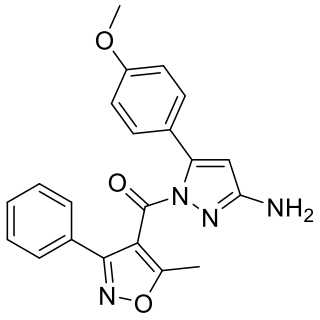
 *N*-(4-isopropylphenyl)-4,5-dihydrothieno[3',2':3,4]benzo[1,2-*d*]isoxazole-3-carboxamide	**66**	ChemDiv	G213-0088
 *N*-[4-(diethylamino)phenyl]-5-(furan-2-yl)-1*H*-pyrazole-3-carboxamide	**SI120**	Enamine	Z317775470
 *N*-(3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-6-yl)-5-phenyl-1*H*-pyrazole-3-carboxamide	**SI121**	Enamine	Z117445894
 *N*-(2,2-difluorobenzo[*d*][1,3]dioxol-5-yl)-5-(furan-2-yl)isoxazole-3-carboxamide	**SI122**	Enamine	Z220530528
 3-methoxy-4-methyl-*N*-[3-(pyridin-4-yl)-1*H*-pyrazol-5-yl]benzamide	**SI123**	Enamine	Z979287910

 *N*-(3-chloro-4-fluorophenyl)-5-(furan-2-yl)isoxazole-4-carboxamide	**SI124**	Enamine	Z1505509423
 *N*-(2-ethyl-2-methylbenzo[*d*][1,3]dioxol-5-yl)-5-(5-methylfuran-2-yl)isoxazole-4-carboxamide	**SI125**	Enamine	Z1873649946
 ethyl 4-(3-phenylisoxazole-5-carboxamido)-1*H*-pyrrole-2-carboxylate	**SI126**	Enamine	Z1286345678
 4-(5-chlorothiophen-2-yl)-*N*-(4-(1,1-dioxidoisothiazolidin-2-yl)phenyl)-1*H*-pyrrole-3-carboxamide	**SI127**	Enamine	Z821502624
 *N*-[3-(thiophen-2-yl)-1*H*-pyrazol-5-yl]benzamide	**SI128**	Enamine	Z759027002
 *N*-[4-(dimethylamino)-3,5-difluorophenyl]-5-(furan-2-yl)isoxazole-3-carboxamide	**SI129**	Enamine	Z810678144

 *N*-[3-(2-oxopyrrolidin-1-yl)phenyl]-5-phenyl-1*H*-pyrazole-3-carboxamide	**SI130**	Enamine	Z117578254
 3-(3-bromophenyl)-*N*-[4-(diethylamino)-2-methylphenyl]-5-methylisoxazole-4-carboxamide	**SI131**	ChemDiv	G794-1887
 *N*-[4-(diethylamino)-2-methylphenyl]-5-methyl-3-phenylisoxazole-4-carboxamide	**SI132**	ChemDiv	C791-0005
 *N*-[4-(diethylamino)phenyl]-5-methyl-3-(pyridin-2-yl)isoxazole-4-carboxamide	**59**	Enamine	Z1437204853
 3',5-dimethyl-*N*-(*p*-tolyl)-[3,5'-biisoxazole]-4'-carboxamide	**SI133**	Maybridge	SPB03214
 *N*-(4-chlorophenyl)-3',5-dimethyl-[3,5'-biisoxazole]-4'-carboxamide	**SI134**	Maybridge	SPB03211

 3',5-dimethyl-*N*-[4-(trifluoromethyl)phenyl]-[3,5'-biisoxazole]-4'-carboxamide	**SI135**	Maybridge	SPB03215
 *N*-(3-chlorophenyl)-3',5-dimethyl-[3,5'-biisoxazole]-4'-carboxamide	**SI136**	Maybridge	SPB03213

[3-Amino-5-(4-methoxyphenyl)-1*H*-pyrazol-1-yl] (5-methyl-3-phenylisoxazol-4-yl) methanone SI137

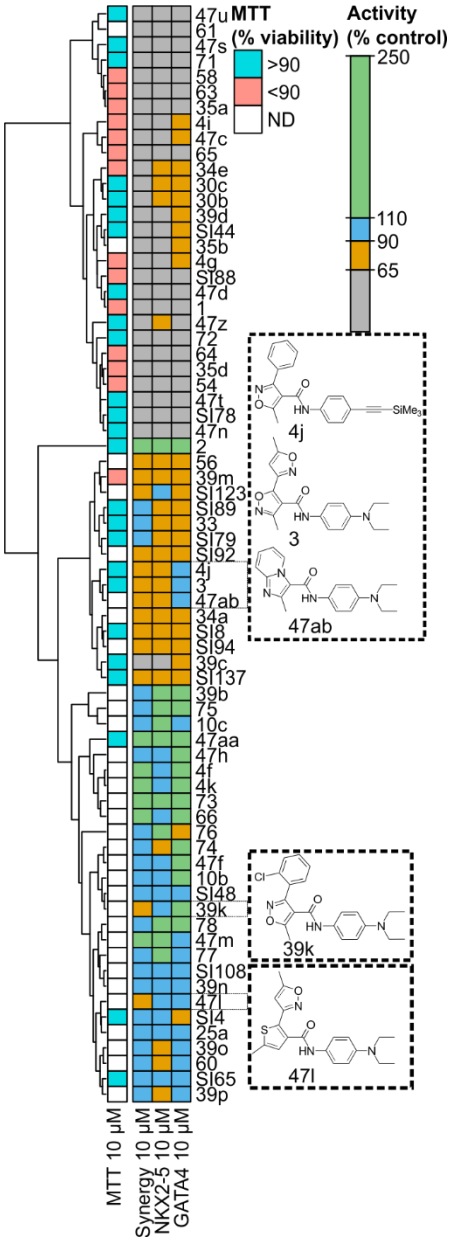


Synthesis previously described[a]

[a]Karhu, S. T.; Välimäki, M. J.; Jumppanen, M.; Kinnunen, S. M.; Pohjolainen, L.; Leigh, R. S.; Auno, S.; Földes, G.; Boije af Gennäs, G.; Yli-Kauhaluoma, J.; Ruskoaho, H.; Talman, V. Stem Cells Are the Most Sensitive Screening Tool to Identify Toxicity of GATA4-Targeted Novel Small-Molecule Compounds. *Arch. Toxicol.* **2018**, *92* (9), 2897–2911.

Hierarchical clustering

To identify compounds which inhibit the GATA4-NKX2-5 transcriptional synergy but have no effect on either NKX2-5 or GATA4 transcriptional activity, we performed hierarchical clustering for biological data to get two-dimensional presentation of the three-dimensional activity data. It has been shown previously[b] that cluster analysis can be used to identify compounds with a similar activity pattern, since they are close to each other in an activity space determined by activity measures. Hierarchical clustering of the activity patterns of selected compounds is presented in SFigure 1. We identified two potentially interesting groups of compounds with different activity patterns based on hierarchical clustering. In the first group, there are two novel compounds which inhibited transcriptional synergy of GATA4 and NKX2-5 without affecting GATA4 transcriptional activity similar to that of compound **3**. In the second group, compounds **39k** and **47l** did not affect NKX2-5 transcriptional activity. In addition, compound **39k** slightly increased GATA4 transcriptional activity at 10 µM concentration. A common structural feature for all selective (i.e. not affecting GATA4 transcriptional activity) inhibitors of GATA4-NKX2-5 transcriptional synergy is a hydrogen bond acceptor in the *para* position in the northern part benzene ring.



Supporting Figure 1. Hierarchical clustering of the activity patterns of compounds. Euclidean distance was used as a distance metric for cluster analysis. The activity of the compound in each luciferase reporter assay is colored according inhibition/enhancement percentage. Color codes: gray (0-65% of control), orange (65-90% of control), blue (90-110% of control), green (110-250% of control. MTT cell viability assay (not used as a parameter in the clustering); red (cell viability >90%), light blue (cell viability <90%) and white not determined (ND).

[b]Xia, M.; Huang, R.; Witt, K. L.; Southall, N.; Fostel, J.; Cho, M. H.; Jadhav, A.; Smith, C. S.; Inglese, J.; Portier, C. J.; Tice, R. R.; Austin, C. P. Compound Cytotoxicity Profiling Using Quantitative High-Throughput Screening. *Environ. Health Perspect.* **2008**, *116* (3), 284–291.